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A MONTHLY JOURNAL DEVOTED TO THE PROBLEMS AND DISEASES OF INFANCY AND CHILDHOOD

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THE DIET OF AN INFANT soon after birth becomes the prime problem in getting the child off to a good start. Variations in the diet must often be based on tolerance, with little attention to vitamin values. Early avitaminosis may develop during periods of dietary adjustment.

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Original Communications

HUNGER EDEMA IN CHILDREN

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INTRODUCTION

THE conditions created by the war and occupation of Greece resulted in the lack of many foodstuffs, particularly animal protein and fat, but also of such items as salt. This resulted in extensive hunger, which was more intense during the winter of 1941-1942 in the urban centers. Large sections of the working and urban middle classes were exposed to prolonged and severe undernourishment, the result of which was the appearance of nutritional edema. This involved at first the members of older age groups, more so the hard working manual laborers. Later on, younger age groups and children were also affected. This gave us the opportunity to secure some clinical and laboratory observations.

GENERAL CONSIDERATIONS

From Sept. 25, 1941, to Feb. 5, 1943, 106 children suffering from hunger edema were admitted to our service. In this group there were sixty-six boys and forty girls. It was of interest that nutritional edema appeared more frequently in males than in females.

Our patients came from the slum and tenement districts of the Athens area, several of them having been brought into the hospital by emergency teams who had found them in a miserable condition in the streets. The largest number of these patients (sixty-seven) was admitted during the October, 1941, to April, 1942, period. Of the total number, sixty-three belonged to the 1- to 3-year-old group which had passed the period of weaning from the breast. Above this age there was a lower incidence of hunger edema, probably due to gastrointestinal adjustment of the older children to the poor quality of food then available, with concomitant lower incidence of gastrointestinal disturbance.

We observed no hunger edema below the age of 6 months. This was probably due to the fact that young infants either received no mother's milk because of lack of supply and thus died, or received basal amounts of human milk and escaped hunger edema. Milk other than human was not available at that time.

From the First Pediatric Service of the Athens University School of Medicine.
This work is dedicated to the memory of Professor G. N. Makkas.

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CLINICAL PICTURE

Infants and children with nutritional edema presented the following clinical picture in our subjects:

There was pallor, marked emaciation, delayed development (particularly in the case of infants), prostration, disappearance of the subcutaneous adipose-areolar tissue, wasting of the muscle masses, and edema. The edema appeared first over the dorsal surfaces of the feet and the ankles and then progressed insiduously to appear over the dorsal surfaces of the hands and over the eyelids. Gradually the edema extended from the ankles to the legs and thighs, from the hands to the forearms and arms, and from the eyelids to the rest of the face. The excessive swelling of the involved parts was in striking contrast to the emaciated edema-free regions of the body. In more severe cases there was extension of the edema to the external genitalia, rising up to the lumbar region. In very severe cases it was generalized. In the case of a 17-month-old boy there was excoriation of the epidermis with oozing of serous fluid. Ascites, hydrothorax, and hydropericardium were often encountered. The body weight of the infants was definitely diminished in spite of the edema, due to severe changes in general nutrition.

The edema was of the pitting type and doughy in nature. It had a tendency to reappear after having responded to nutritional measures, usually in connection with gastrointestinal disturbances.

The overlying skin was shiny, pale or bluish red. We observed frostbites over the affected areas with ulceration in two patients and with gangrene of nose and one big toe in one patient. A fine desquamation of the epidermis particularly over the chest was seen repeatedly. Furunculosis was common, and on some rare occasions we observed hemorrhagic macules and bruises (seven children). Pellagroid rash was found over the extremities of four patients, due to co-existing avitaminosis.

Ophthalmological examination revealed xerophthalmia in three children and keratomalacia in one. The co-existing rachitic manifestations were attributed to pre-existing vitamin D deficiency.

Hypothermia was a common sign.

The lungs showed bradypnea with wet râles over the bases and ronchi over the rest of the field.

The cardiovascular system showed distant heart sounds, bradycardia, and hypotension.

Gastrointestinal disturbances were common. Nine patients had diarrhea stools, fourteen had mucous ones, and in four mucosanguineous excreta were encountered.

The urinary system showed polyuria and evidence of renal irritation in ten cases.

The nervous system was free from abnormal manifestations and the sensorium was clear even in the severest cases.

The blood showed moderately low red blood cell counts, low hemoglobin, leucopenia with lymphocytosis, and severe hypoproteinemia with low blood urea.

Tuberculin tests after Mantoux were positive in dilution 1:10,000 in twenty-four out of 106 cases.

In spite of our efforts to secure more extensive laboratory studies, we found this impossible, due to lack of even the most elementary reagents.

The prognosis of this syndrome depends upon: (a) the degree of malnutrition; (b) the co-existence or delayed appearance of complications; and (c) the possibility for correction of the nutritional staus. Out of our 106 patients, eighty-one were cured (76.42 per cent) and twenty-five died (23.58 per cent). This mortality rate includes malnutrition and co-existing diseases. The disappearance of edema occurred in the uncomplicated cases during the first fourteen days and on the average on the thirteenth day of admission, following gradual restitution of food intake on the basis of age.

With reference to the pathogenesis of nutritional edema, several explanations have been forwarded. Of these the most widely quoted ones are: (1) the theory of altered capillary permeability due to lipoid deficiency, lipoids being essential for capillary function; (2) the excessive salt and water intake with storage of both in the tissues; and (3) hypoproteinemia.

HYPOPROTEINEMIA AND HUNGER EDEMA

The purpose of this investigation has been the establishment of: (1) the immediate relationship of hunger edema to the diminution of total serum protein (TSP) below normal levels; (2) the immediate effect of animal protein on the re-establishment of normal TSP values, (3) the immediate effect of re-establishment of the normal TSP values on edema.

We specifically investigated forty out of the 106 patients with these aims in mind. These patients we divided in three groups: Group A, comprising thirty-three children in whom we determined the serum proteins during the period of qualitative and quantitative nutritional improvement until the good or bad outcome; Group B, comprising four children in whom we investigated the effect of food containing normal amount of calories free from animal protein on the TSP level; Group C, comprising three children in whom we investigated the effect of special animal proteins on the re-establishment of normal serum protein levels by using milk, egg white, and egg yolk.

To complete the observations and to verify our impressions we produced nutritional edema in a group of three normal children by withholding animal protein from the diet.

The determinations of TSP were done by the refractometric method of Robertson. This method is simple, quick, and easy but has the disadvantage of being influenced by abnormally high urea, lipoid, and sugar concentrations in the blood. In our cases, however, these substances, with possible exception of fat, were encountered in subnormal amounts. We believe, therefore, that our results can be considered as accurate.

Group A.—The TSP after admission of thirty out of thirty-three patients was determined (a) on twelve during the first day (b) on thirteen during the second, and (c) on five during the third day. The values of TSP were as follows: subgroup (a) had an average of 4.42 and in six cases was below 4.0 Gm. per 100

Fig. 1.—Showing edema and skin rash.

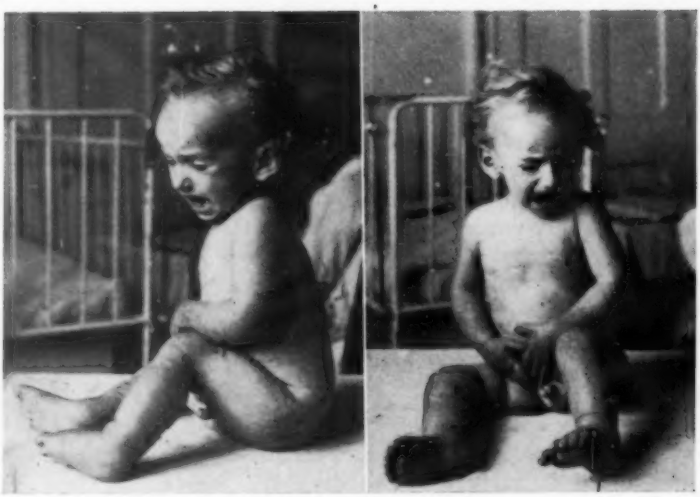

Fig. 2.—Showing edema and skin rash.

Fig. 3.—Showing edema and skin rash.

Fig. 4.—Showing edema, skin rash, and emaciation.

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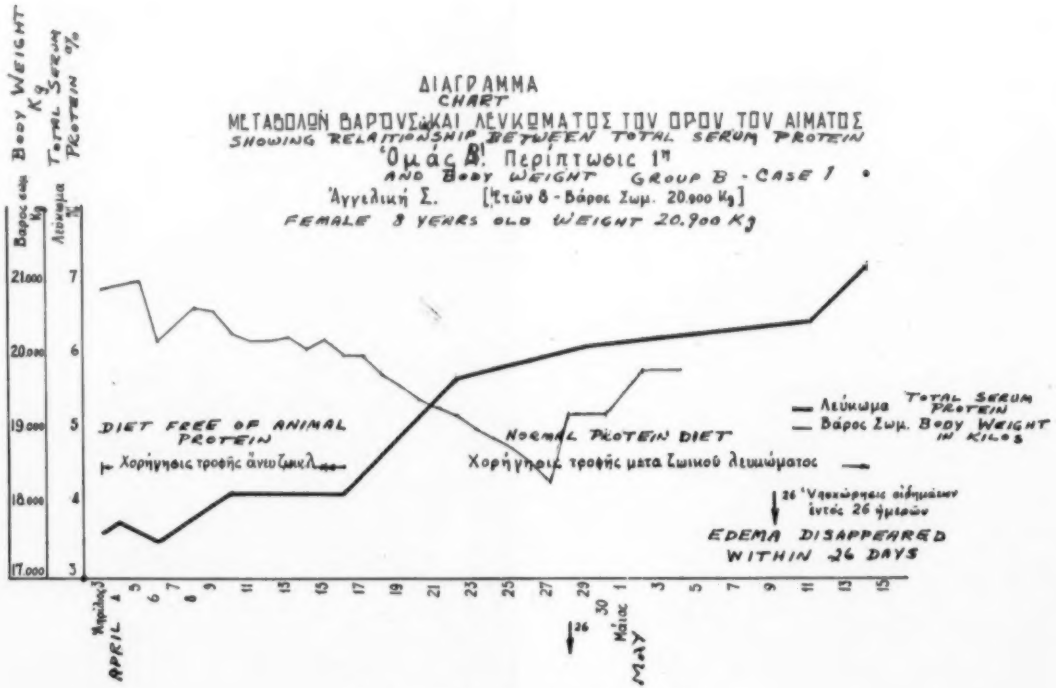

Chart I.—Illustrating Case 1, Group B.

c.c.; subgroup (b) had 4.37 Gm. per 100 c.c. on the average; subgroup (c) had 4.94 Gm. per 100 c.c. on the average. In relation to age, subgroup (a) included seven patients from 9 months to 3 years who averaged 4.56 Gm. per 100 c.c. and five patients from 4 to 10 years who averaged 4.24 Gm. per 100 c.c.. In subgroup (b), ten children were 10 months to 3 years old and had an average TSP of 4.45 Gm. per 100 c.c.; three children were 4 to 8 years old and averaged a TSP of 4.12 Gm. per 100 c.c. In subgroup (c) there were five patients 22 months to 3 years old who had average TSP of 4.94 Gm. per 100 c.c.

These observations reveal that (1) the TSP was considerably below normal (5.90 Gm.) on admission, with the exception of two children who were low normal. In all the others (twenty-eight) TSP was below normal, ranging from 2.84 Gm. per 100 c.c. to 5.68 Gm. per 100 c.c. (2) The higher serum proteins in the cases of children from 9 months to 3 years of age as compared to the 4- to 10-year-old children is probably due to the fact that larger amounts of animal protein had been administered to the younger children in the form of milk.

These thirty-three children were given gradually increasing doses of food orally until the optimum was reached. During this period we determined the TSP repeatedly. The determinations showed continuously increasing values which reached normal levels within eleven to twelve days on the average. At the same time there was a parallel decrease in body weight with diminution of the edema, which disappeared in thirteen to fourteen days. This demonstrates the relationship between normal food intake and TSP on the one hand, and TSP level and edema on the other.

Group B.—The effect of animal protein on hunger edema was investigated in four children who were given no animal protein. In three of these, animal protein was withheld for thirteen, sixteen, and nine days, respectively. This time period was adequate to reduce the edema in the patients of the previous group, who received a complete diet. The animal protein-free food which was otherwise complete in terms of other foodstuffs, caloric contents, and was supplemented by vitamins, had little effect on the serum protein level of the two first children while in the third there appeared a diminution of TSP from 4.92 to 3.94 Gm. per 100 c.c. The body weight diminished to some extent in the first child (8 years old), with some amelioration of the edema, but remained stationary in the second (5 years old), and increased considerably in the third (3 years old), with aggravation of the edema.

These observations demonstrate the necessity for more animal protein in younger children. No gastrointestinal disturbance appeared in any of the patients.

Following the above specified periods of observation, animal protein (milk, eggs, cream) was added to the diet at the expense of carbohydrate and fat by keeping the caloric intake stable. Soon after the administration of animal protein there was a rapid and continuous increase of TSP. The latter reached normal levels with concomitant rapid loss of edema, which disappeared after serum levels reached normal. This is in contrast to the views forwarded by Maase and Zondek,[15] who attributed hunger edema to the lack of fat and lipoid.

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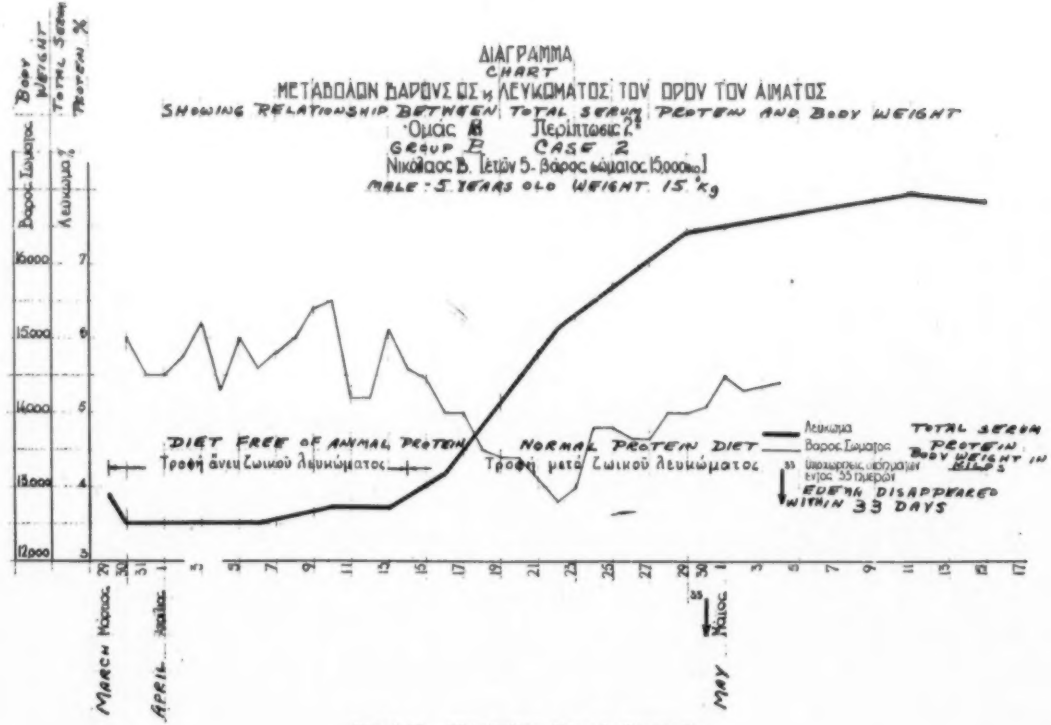

Chart II.—Illustrating Case 2, Group B.

In the fourth of these patients (aged 10) the patient received no animal protein but was given a high caloric intake high in vegetable protein. After the seventh day on this diet there appeared an increase in TSP with fall in body weight and diminution of edema. After fourteen days the TSP reached normal and the edema disappeared. This case demonstrates that older children can lose the edema when given large amounts of vegetable protein two or three times the equivalent amounts). It is noteworthy, however, that, although from the fifteenth to the twenty-third day the patient was on the same diet, his TSP diminished from 6.98 to 6.12 with concomitant increase in body weight, meaning probable water retention. After the twenty-third day he was given a lower caloric intake with added animal protein, which resulted in increase in total protein to 8.06, twenty days later. This was followed by amelioration of general nutrition and disappearance of edema.

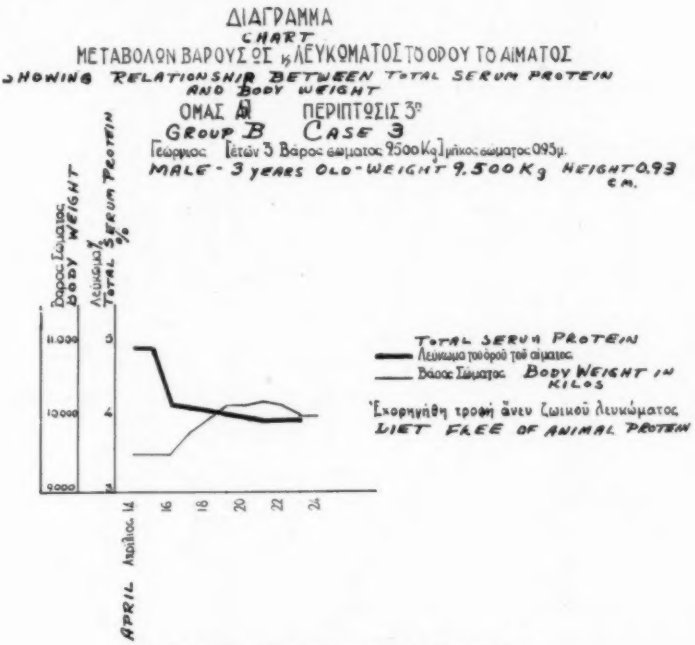

Chart III.—Illustrating Case 3, Group B.

Group C.—(Three cases) The first patient received milk and sugar in amounts covering the caloric needs for weight and age for eleven days. The amount of protein was twice the required and that of carbohydrate and fat was normal. The second patient received ten egg whites prepared with sugar, containing adequate amounts of calories, markedly excessive protein, and small amount of carbohydrate for seventeen days. The third patient was offered five egg yolks daily and 75 Gm. of sugar, which made an adequate diet from caloric protein, carbohydrate, and fat viewpoint.

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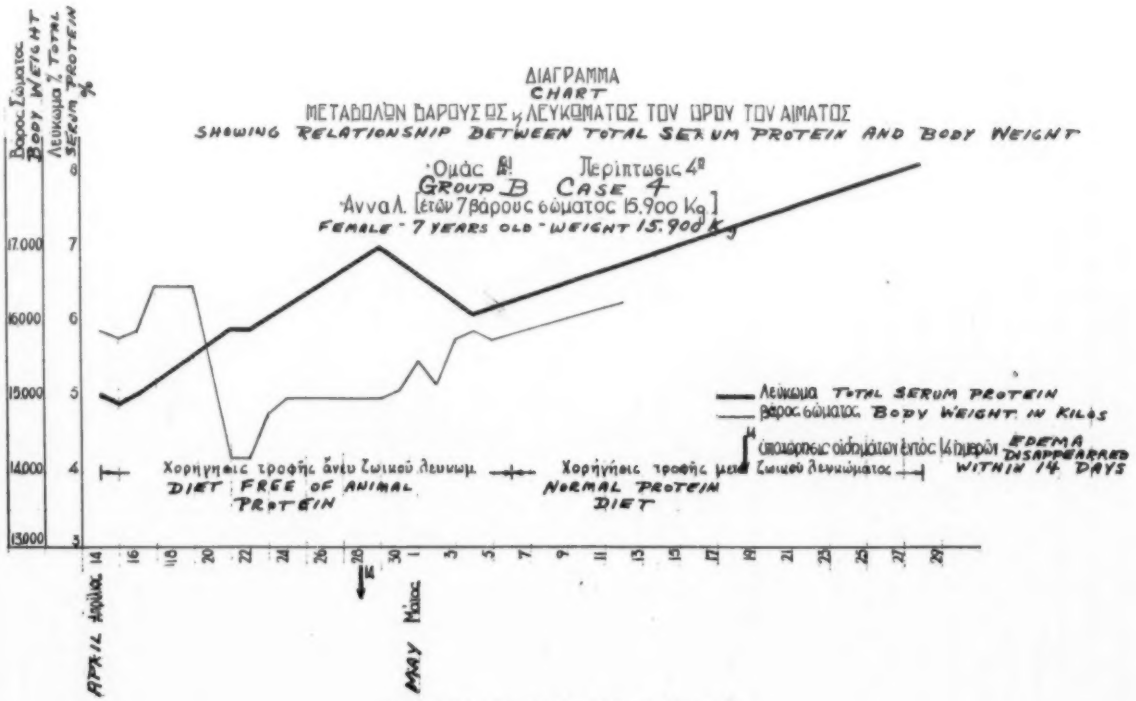

Chart IV.—Illustrating Case 4, Group B.

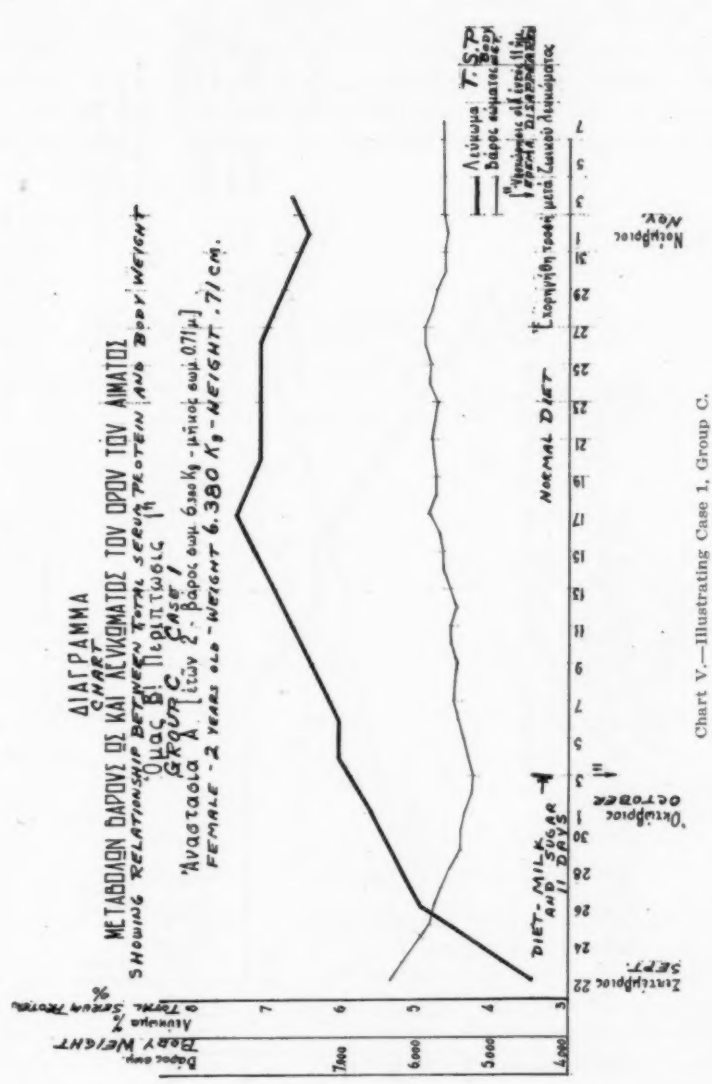
ΔΙΑΓΡΑΜΜΑ
CHART
ΟΜΑΣ Β' ΠΕΙΡΑΜΑΤΟΣ 1η
GROUP C. CASE 1
Ανασταλία Α' [ετών 2. βάρος σωμ. 6.380 Κg - μήκος σωμ. 0.71 μ.]
FEMALE - 2 YEARS OLD - WEIGHT 6.380 Kg - HEIGHT .71 cm.
DIET - MILK AND SUGAR 11 DAYS
NORMAL DIET
Σεπτ. Sept.
Οκτ. October
Νοε. Nov.
Βάρος σωματος Body Weight
Ολικη πρωτεϊνη ορου αιματος Total Serum Protein
T.S.P.

Chart V.—Illustrating Case 1, Group C.

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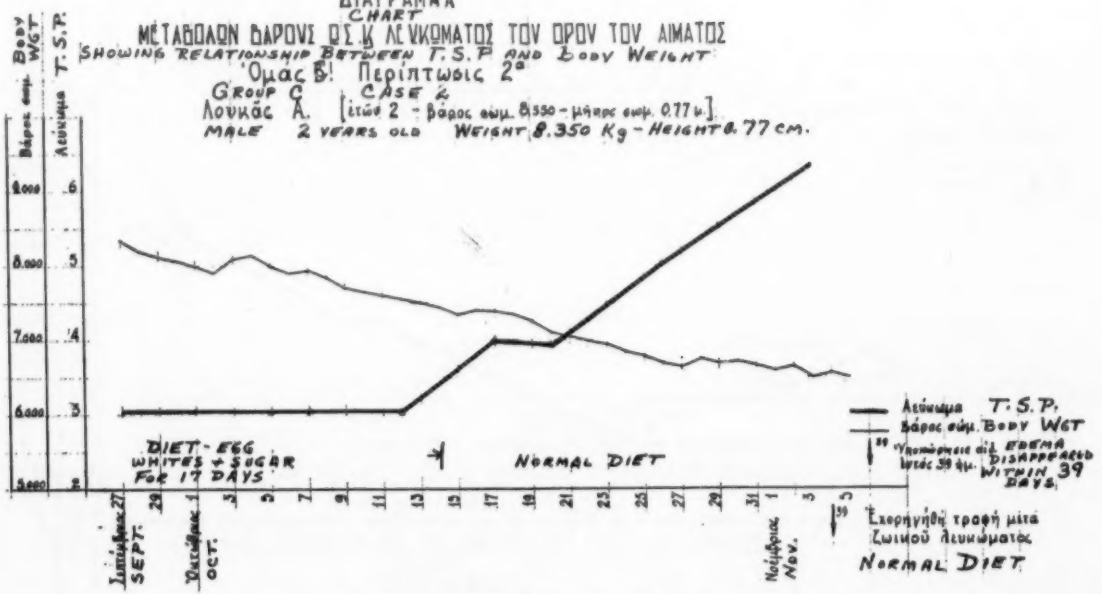

Chart VI.—Illustrating Case 2, Group C.

In the first case the TSP determinations revealed a constant increase in serum proteins with concomitant disappearance of edema within eleven days as soon as the serum level reached normal. In the second case we obtained four determinations during twelve days of observation which revealed a constant TSP value of 3.06 Grams. His body weight showed minor fluctuations while his marked edema showed no amelioration. On the thirteenth day we interrupted the egg white-sugar intake and gave a normal diet, which resulted in disappearance of the edema. In the third patient there was a continuous

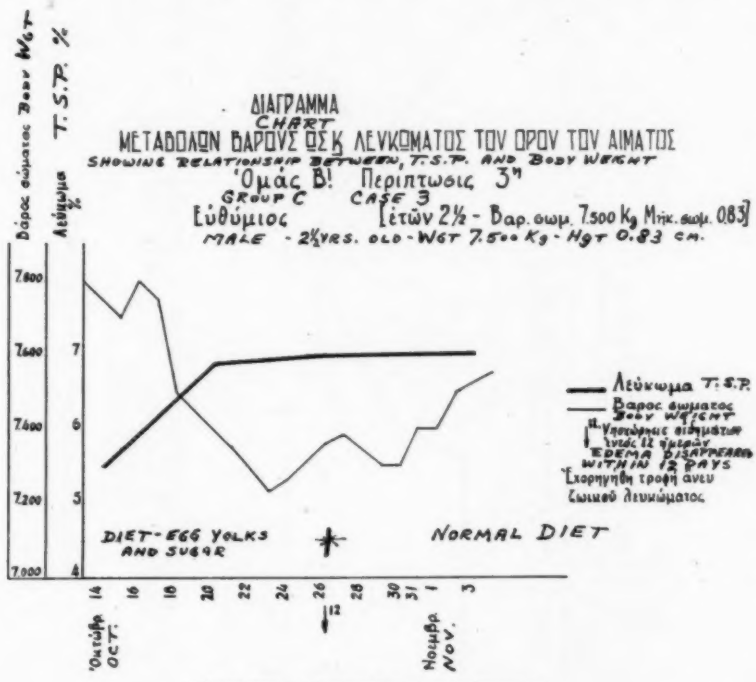

Chart VII.—Illustrating Case 3, Group C.

increase in serum protein and continuous loss of edema with decrease of body weight. These observations show again the dependence of nutritional edema on the TSP, the effect of animal protein on the latter, and the immediate effect of the TSP on the course of the disease. A noteworthy exception was encountered during the administration of egg white and sugar. This may be attributed either to lack of absorption of this protein under the circumstances of administration in the absence of a proper carbohydrate-fat-protein ratio or in the specific dynamic action of the protein.

In order to complete this study we produced nutritional edema in three normal children by withholding animal protein from the food. These form a fourth group in our series.

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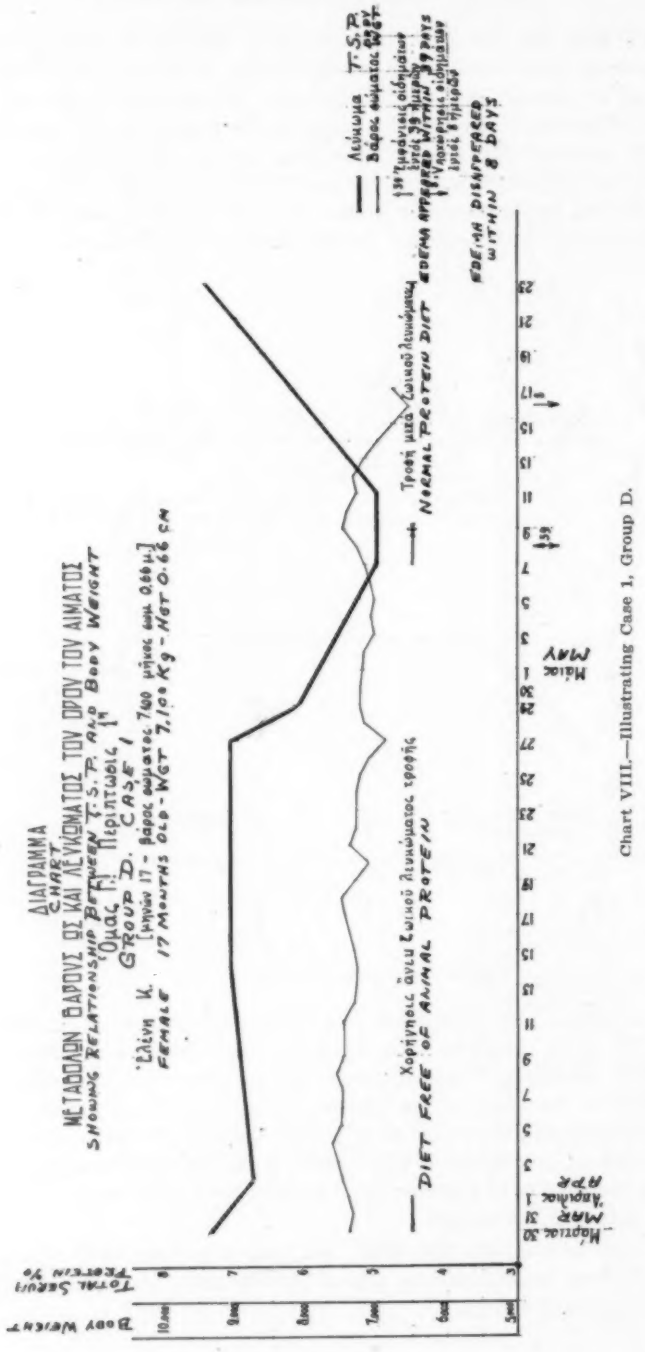

Chart VIII.—Illustrating Case 1, Group D.

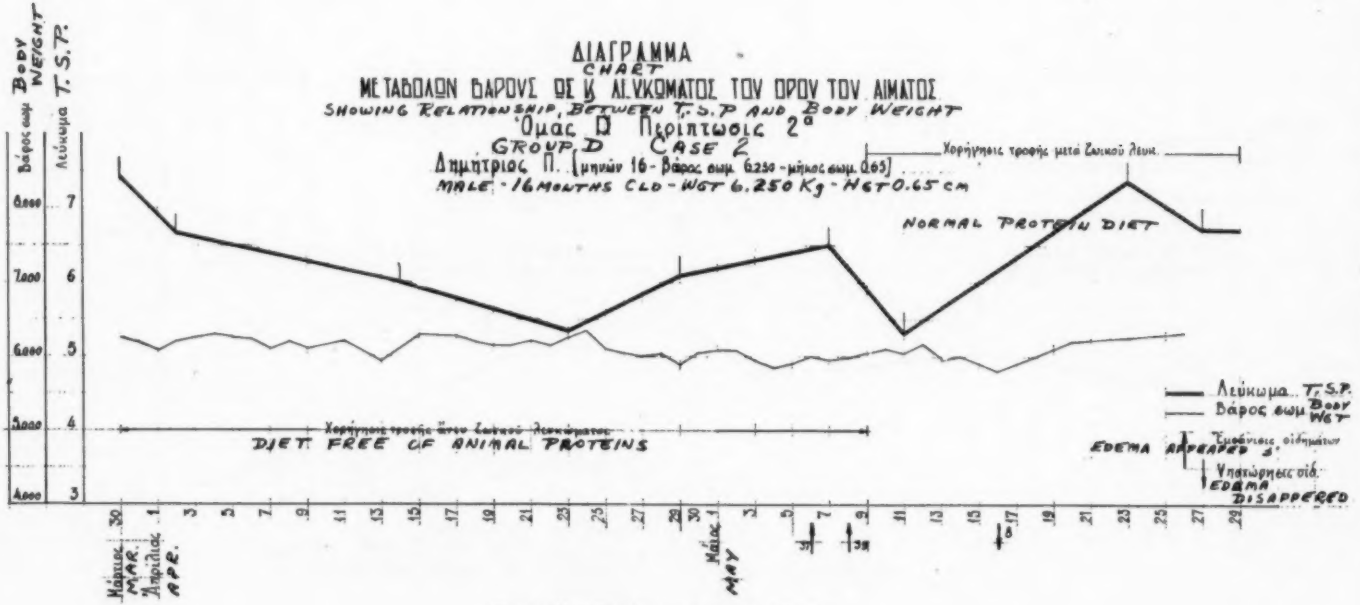

Chart IX.—Illustrating Case 2, Group D.

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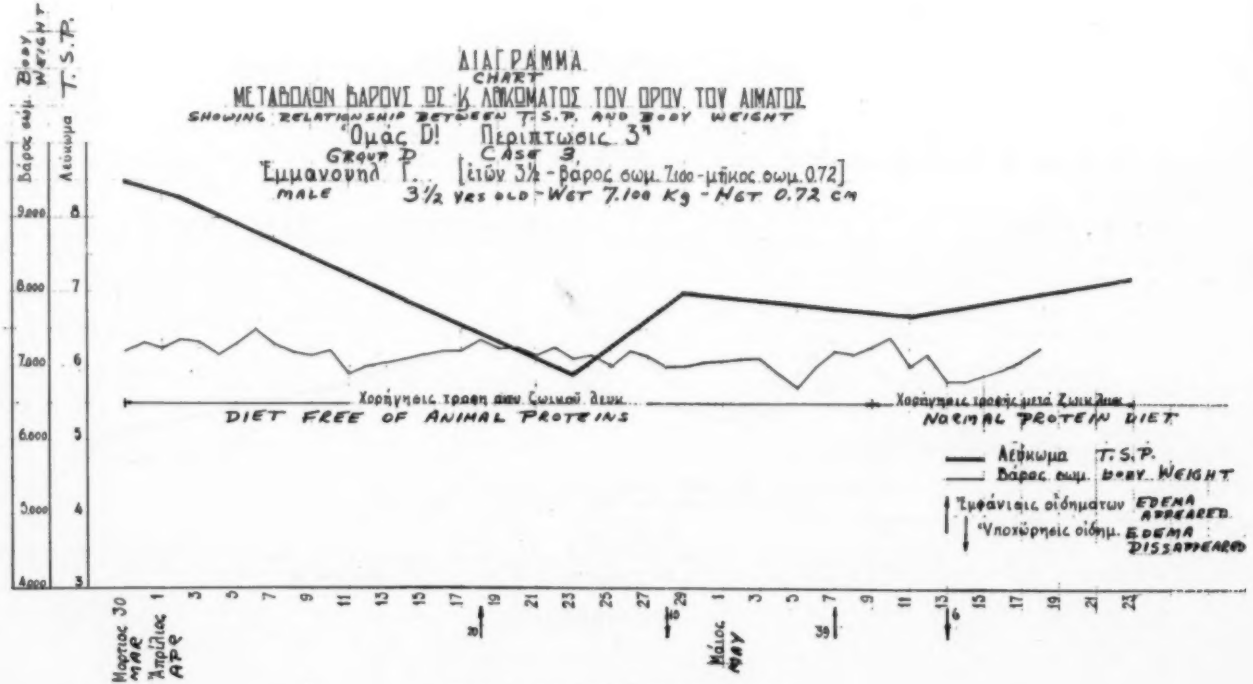

Chart X.—Illustrating Case 3, Group D.

Group D.—In these three children who received small amounts of vegetable protein and no animal protein, we found at the onset of the observations normal TSP values, namely 7.42 Gm. per 100 c.c. in the first and second cases and 8.49 Gm. per 100 c.c. in the third. The daily food intake contained a sufficient number of calories. The protein content was inadequate in opposition to fat, which was more than adequate. The carbohydrate content was slightly below normal values. In addition, vitamin B complex was given parenterally. During the progress of the observations our repeated serum protein determinations revealed a continuous drop in the serum protein level. Values below normal were encountered in the first patient on the thirty-eighth day (5.03 Gm.), in the second on the twenty-fourth day (5.26 Gm.), and in the third on the twentieth day (5.03 Gm. per 100 c.c.). During this period there was a fall in body weight. A few days before the appearance of edema the weight increased. Concomitantly with the above phenomena there appeared insidiously increasing weakness, pallor, emaciation, diminution of subcutaneous adipose tissue, polyuria, bradycardia, and arterial hypotension. During the thirty-ninth day in the first patient, the thirty-seventh in the second, and the twentieth in the third, there appeared dependant edema over the lower extremities. This became more marked during the supervening two days in the first two patients. In the third the edema disappeared on the tenth day and re-appeared again on the thirty-ninth day to become more pronounced during the superseding two days. On the average the hypoproteinemia appeared on the twenty-seventh to thirty-eighth day while the appearance of edema occurred on the thirty-second day after the withdrawal of animal protein from the food. From the fortieth day on in the first two patients and the forty-first day in the third, we interrupted the above regimen and administered animal protein. A few days later we observed an increase in TSP and the body weight decreased while the edema diminished. This latter disappeared seven days later in the first two children and six days later in the third. At this point the serum proteins value were of normal value.

CONCLUSIONS

1. The nutritional edema is due to hypoproteinemia and the resulting low osmotic value, which in turn results in the exit of water from the blood to the tissues.

2. There is a direct relationship between the degree of hypoproteinemia and edema.

3. In the younger children there is an absolute necessity for animal protein, while in older age groups large amounts of vegetable protein, ranging from two to threefold the normal values, may induce a temporary improvement.

4. Egg white alone was demonstrated to have no effect on hypoproteinemia and nutritional edema, in opposition to milk and egg yolk.

5. Other factors such as changes in capillary permeability, lack of fat, avitaminosis, excessive salt and water intake, have only a contributory significance.

6. The susceptibility to nutritional edema is more marked in the case of boys as opposed to girls.

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SUBLINGUAL METHYL TESTOSTERONE FOR BOYHOOD EMOTIONAL, PHYSICAL, AND GENITAL IMMATURITY

FLOYD E. HARDING, M.D.
LOS ANGELES, CALIF.

METHYL testosterone enlarges all parts of the male genitalia before or during puberty. It increases the size of the testicle to some extent although there is greater growth in the penis, scrotum, vas deferens, and prostate. When small doses of it are given, however, it does not initiate the onset of puberty in a child too young for this occurrence.

In boys with unusually small genitalia, a neurosis may be caused by the fear of abnormality and by the cruelty of other children who make disparaging remarks. This condition is easily cured with methyl testosterone without apparent harm.

Observation of the marked benefit obtained in the treatment of neurosis due to undersized genitalia prompted the trial of methyl testosterone for patients of a similar type with poor muscular development and an emotional response like that of a younger child. After a good initial result in a few patients, it seemed desirable to give a group of immature boys methyl testosterone to note its general effect. Other clinicians have reported benefit with this type of treatment.[1-3, 11, 13-14] Publications have also shown that this androgen increases the rate of growth in short individuals,[2, 3] and that the creatine excretion is increased.[4] There is said to have been improvement in the muscular performance of older men.[12]

Extensive oral use of steroid substances in the female has given information on the variation in absorption and effect of these preparations and has helped in evaluating the response with methyl testosterone when given to boys.[7-10]

METHOD OF TREATMENT

The sublingual method of administration was chosen because the hormone was said to be a little more effective when used in this manner instead of being swallowed.[16] The tablets of methyl testosterone* were held under the tongue or between the teeth and the cheek and allowed to dissolve slowly to obtain as much local absorption as possible. They each contained 5.0 mg. of material and were cut in half or in fourths for the 2.5 mg. or 1.2 mg. doses. The total daily dose given each patient is found in Table I.

Treatment was given continuously up to two months, after which, if further development was required, the medication was discontinued for one month, then given another two months. This precaution, although probably unnecessary with the small doses used, was taken in order not to upset other glandular function over too long a period.

From the Department of Endocrinology, Ross-Loos Medical Group, Los Angeles, Calif.

*The Metandren Linguets (methyl testosterone) were obtained from Ciba Pharmaceutical Products, Inc., Summit, N. J.

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The obese patients were given a low-caloric vitamin-rich diet made up largely of fruits and vegetables but containing sufficient protein for a growing child. The underweight children were given a high-caloric vitamin-rich diet.

CLINICAL MATERIAL

All of the patients treated had small genitalia. The penis and testes were small, and the scrotum was also underdeveloped. The fat mons frequently covered the penis, causing urination to be difficult and embarrassing. There were cases of pseudo- and true cryptorchidism. All of the children and their parents believed that the condition was abnormal and that improvement in size was desirable if it could be obtained. Several of the children had a neurosis wholly or partly due to the cruelty of other children laughing or making remarks about the infantile nature of their organs. Many boys were emotionally immature or physically weak. Some complained of enuresis. Failure in school or very poor work in spite of good intelligence was often reported. At times growth was a problem, as the height age was less than the chronological age. It was believed that the small size of the genitalia on examination was usually insufficient reason for therapy, unless some other physical or psychological abnormality existed; and in most children treated two or three indications were found to be present. Further details can be found in Table I.

RESULTS

Genital development was considered satisfactory in all patients taking methyl testosterone. The penis increased in size more rapidly than the testicles but the latter became definitely larger also. There was no evidence of testicular atrophy. These glands were of normal shape and firmness after treatment. The medication was discontinued when the penis became large enough to be considered within the limits of normal and about average size for the height and general development of the child. No attempt was made to enlarge the penis beyond what was considered normal. In the obese patient, reducing the size of the fat mons and enlarging the penis greatly improved the physical appearance and facilitated urination and cleanliness. The scrotum became more pendulous and rugose. There was an increase in length of the ductus deferens and some development of the prostate. The testicles stayed down better in the pseudocryptorchid patients and in four boys with true cryptorchidism a cure was effected. One boy with cryptorchidism and inguinal hernia had an operation. Three of the older boys began to have nocturnal emissions. Those going through puberty had an increase in the amount of pubic hair. In the younger children there was no growth of pubic hair. There was great variation in the rapidity of development. Some boys developed in two to three months with very small doses of methyl testosterone, whereas other boys developed slowly with larger doses. In general the very short children or those with very small testicles required longer treatment.

Methyl testosterone definitely increased the rate of growth. During treatment and in the months immediately following medication the entire group of fifty-eight children averaged 3.2 inches growth per year per individual. Sixteen

TABLE I. CLINICAL MATERIAL AND THE DOSAGE OF METHYL TESTOSTERONE

CASE NO.	AGE	HEIGHT (INCHES)	WEIGHT (LB.)	BODY TYPE	PENIS COVERED	SIZE OF GENITALIA	PHYSICALLY WEAK	EMOTIONALLY IMMATURE	MISC.	REDUCING DIET	(MG.) DOSE DAILY	MONTHS OF TREATMENT
1	11	63.0	120	O	Pc	G	—	I	—	D	2.5	2.0
2	2	33.0	30	O	Pc	G	—	—	—	—	1.2	2.4
3	10	52.5	66	N	—	G	W	—	S	—	2.5	4.0
4	13	62.0	158	O	C	V	—	I	—	D	10.0	2.9
5	14	57.7	101	O	—	G	—	—	S	—	2.5	20.0
6	13	61.5	125	O	Pc	G	—	I	—	—	5.0	2.0
7	12	64.0	173	O	—	V	W	I, F	—	D	5.0	2.7
8	7	46.0	43	N	—	V	—	I, F	S, E	—	2.5	4.0
9	13	62.5	126	O	C	V	W	—	—	D	5.0	6.0
10	11	62.0	120	O	Pc	G	W	—	—	D	5.0	3.0
11	11	59.7	107	O	—	G	—	I, F	M	—	5.0	6.6
12	12	63.5	150	O	C	V	—	I	—	D	5.0	6.0
13	9	53.0	108	O	—	V	—	I	M	D	5.0	3.2
14	9	54.2	77	O	—	G	W	I, F	Cr	—	2.5	6.0
15	11	56.0	105	O	—	G	W	I, F	—	D	5.0	1.4
16	1	29.0	25	O	C	V	—	—	—	D	.6	1.8
17	12	60.0	124	O	Pc	G	—	I	—	D	5.0	2.3
18	16	61.7	96	U	—	V	—	—	S	—	5.0	8.0
19	12	65.2	185	O	C	V	—	—	Ga	D	5.0	13.0
20	11	54.0	58	U	—	V	—	—	S	—	10.0	5.0
21	12	60.5	122	O	Pc	G	W	—	—	D	5.0	2.0
22	8	54.6	104	O	C	V	—	I	—	D	5.0	6.5
23	12	59.0	106	O	C	V	W	—	—	—	5.0	3.0
24	15	63.0	106	N	—	G	—	I	—	—	5.0	6.0
25	9	59.2	134	O	Pc	G	—	—	Cr	D	5.0	1.8
26	1	29.5	25	O	C	V	—	—	—	—	1.2	3.7
27	13	64.7	130	O	—	G	—	I, F	Cr	D	5.0	7.0
28	10	52.5	91	O	—	G	—	—	S	D	2.5	6.0
29	12	58.5	84	N	—	V	—	I, F	—	—	5.0	8.1
30	9	57.0	117	O	C	V	W	—	—	D	5.0	4.8
31	1	28.0	24	O	C	V	—	—	—	D	2.5	2.3
32	10	56.7	81	N	—	G	—	I, F	E	—	2.5	3.0
33	12	62.5	105	O	Pc	V	W	I, F	—	—	5.0	1.4
34	10	54.0	105	O	Pc	G	W	I, F	—	D	1.2	5.2
35	10	56.0	93	O	Pc	V	—	I, F	—	D	10.0	3.2
36	9	53.0	64	N	—	G	—	—	M	—	5.0	2.2
37	8	52.7	77	O	—	G	—	I, F	—	D	2.5	4.0
38	11	56.7	87	O	—	G	W	I	—	D	5.0	5.0
39	11	61.0	114	O	Pc	G	—	—	Cr	D	5.0	5.0
40	11	61.0	118	O	Pc	G	—	—	E	D	2.5	2.4
41	11	62.5	106	O	—	G	—	—	Gy	D	5.0	2.1
42	11	59.0	98	O	C	V	W	I, F	Gy	D	5.0	3.9
43	14	56.7	80	N	—	G	W	I	S	—	5.0	6.8
44	13	58.5	86	N	—	G	—	—	S	—	5.0	2.8
45	14	64.5	128	O	—	G	W	I	Gy	D	5.0	4.0
46	13	61.2	126	O	C	V	—	I	—	D	5.0	1.4
47	7	52.0	84	O	—	V	—	—	Cr	D	2.5	2.8
48	10	51.2	59	N	—	G	W	I	S	—	2.5	2.0
49	10	57.5	104	O	Pc	G	—	I	—	D	5.0	2.7
50	8	54.5	73	N	—	G	W	I, F	E	—	1.2	9.3
51	12	56.0	74	N	—	G	W	—	S	—	2.5	4.5
52	12	59.0	107	O	Pc	G	W	F	—	D	5.0	2.0
53	14	61.5	110	O	Pc	V	—	I	S, Gy	D	5.0	9.9
54	15	69.2	178	O	Pc	G	W	I	E	D	5.0	2.2
55	11	58.5	113	O	Pc	G	W	—	E	D	5.0	1.2
56	13	61.5	160	O	C	V	—	—	Gy	D	5.0	4.0
57	9	58.0	105	O	C	V	W	I, F	—	D	10.0	9.0
58	13	63.0	93	U	—	G	W	I	—	—	2.5	2.0

O, obese; N, normal weight; U, underweight; C, penis covered by fat mons; Pc, penis partly covered by fat mons; S, too short; E, enuresis; Gy, gynecomastia; I, emotionally immature; acts like younger child; W, physically weak; poor muscular development; F, poor school work; failing in spite of average intelligence; D, reducing diet; G, genitalia smaller than average; V, genitalia very small; Cr, cryptorchidism; M, migrating testicle (pseudocryptorchidism).

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controls, ages 8 to 15 years, of essentially the same endocrine types, were not given methyl testosterone and they grew on an average of 2.3 inches per year. The average boy from 8 to 14 years of age grows 2.2 inches per year. The eleven short boys receiving methyl testosterone grew 3.3 inches per year on an average. This was faster than they grew in the year prior to taking methyl testosterone according to their own statements, although exact measurements were not available. Their appearance was good after treatment as growth was proportionate.

Physical improvement was frequently outstanding, especially in the weak, flabby, obese boy who was often somewhat effeminate, and in the thin child with little muscular development and stamina. The shoulders broadened, the muscles in the neck, back, and shoulders becoming definitely larger. The greater shoulder breadth made the relation between shoulders and pelvis more like that of the adult man. There was also some improvement in other skeletal muscles; more work could be done without tiring; physical tasks were performed with greater speed and facility. The boys played better, because now they occasionally won games; they frequently gave up playing with younger children. The feet and hands became larger. There was usually some gain in weight except when the patient was following a reducing diet. Quite naturally, this increase in pounds was more striking in the thin individual.

Other noticeable improvements showed in the lessening of the feeling of inferiority and of the exhibition of emotional immaturity; the children cooperated better with parents and teachers and took more responsibility. They were less inclined to act like younger children and became more amenable to reason, showing an improvement in their personalities. To some extent they seemed to mature psychologically and became more dependable, causing their actions to be more predictable. The children in this group were normal mentally, yet failure at school was common. The school work improved with lessening in nervousness and restlessness, while there was an upward trend in concentration and attitude. Bad childhood habits were more easily broken; enuresis was cured in two and improved in two of the six patients who had not broken this tendency.

Most of the children were observed for from one to four years following completion of treatment. They continued to develop normally. A few were given another course or two of treatment. They did well when compared with nontreated patients previously observed. Epiphyseal closure came at the expected time.

UNDESIRABLE EFFECTS

No bad effects were noticed except for sexual stimulation in three patients who had the masturbation habit. These boys knew beforehand that the tablets might cause more frequent erections. Treatment was stopped and later resumed with smaller doses. The others had no knowledge of the physiologic effects of the tablets and were untroubled with the small doses given. The tablets caused some of the boys to have acne of a minor nature.

No allergy or idiosynerasy was encountered. It was observed that methyl testosterone was well tolerated by the gastrointestinal tract.

DISCUSSION

Taking everything into consideration the results were quite satisfactory and often impressive.

A note of warning is due here. It is not intended to imply that methyl testosterone is a cure for psychoneurosis, weakness, or underweight. The only neurosis cured by its administration was the one due to embarrassment caused by the small genitalia, although the children frequently became less emotionally immature. All patients showed enlargement of the penis, but only part of the patients in this carefully selected group had improvement in weight, muscular development, and growth greater than would be expected without treatment.

It must be kept in mind that most cases of cryptorchidism, cases of abnormality of the genitalia other than smallness of size, and most other endocrine disorders were not included in the series treated with methyl testosterone. Some boys age 16 to 21 were seen whose genitalia did not improve to the extent of being within the range of normal size. Older children diagnosed as eunuchoids were not included in the group reported here; those treated usually responded more slowly and required larger daily doses than the boys in this group. In adults, the most effective form of substitution therapy was found to be the implantation of testosterone pellets, although other methods were satisfactory.[5]

Anterior pituitary-like substance appears to be better than methyl testosterone for the treatment of cryptorchidism.[6] However, the two are sometimes combined where there is marked underdevelopment. If anterior pituitary-like substance is used instead of methyl testosterone, there is greater growth of the testicle and less enlargement of the penis. After the testicle increases in size, it produces more testosterone, which in turn causes some growth of the other parts of the male genitalia.

It is frequently argued that treatment is unnecessary as the genitalia become normal with puberty and all one need do is to wait. This reasoning is superficial as it does not consider the possibility that the handicapped child may develop into a neurotic adult or a poor citizen. The physical or emotional immaturity results in poor play and school work. The child grows up into an adult having failed to learn how to get along satisfactorily with other people. Since enuresis also may be due to physical and emotional immaturity, treatment with methyl testosterone at an early age may cure those boys who would improve spontaneously years later at puberty.

How the adult size of the genitalia of the fifty-eight patients treated would compare with the adult size of a similar group used as a control is unknown at the present time.

Testosterone propionate is believed to inhibit spermatogenesis temporarily in adults.[15] However, before puberty there is a physiologic lack of spermatozoa formation. None of the boys in this group had had any semen at the time treatment was instigated. Also, the dosage used was much smaller than that required for inhibition of spermatogenesis.

Although small doses of methyl testosterone increase the size of the penis and testicles in the child, a dosage of 20 mg. daily has no effect on the size of these organs in the normal adult. Some improvement is obtained in the size

of the atrophic penis, accessory genitalia, and secondary sex characteristics if treatment is begun after atrophy of the testicles from mumps, injury, hernia operation, infection, or irradiation, or after castration.

CONCLUSIONS

Methyl testosterone was administered in small daily doses to a carefully selected group of fifty-eight children, mainly between the ages of 7 and 15 years. The sublingual method was used.

Satisfactory development of primary and secondary sex characteristics occurred. In some patients there was an increase in weight and production of greater muscular strength. The average rate of growth as determined by height was increased to 3.2 inches per year. The neuroses due to the presence of very small genitalia were cured. There was less emotional immaturity.

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CEREBRAL COMPLICATIONS IN PERTUSSIS

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INTRODUCTION

PERTUSSIS is still a challenge to the medical profession, especially when it occurs in infants under one year of age. Of all the infectious diseases none is more important from the point of view of morbidity and mortality. The disease is most serious when complicated by pulmonary or cerebral manifestations.

Over 200,000 cases of whooping cough are reported annually in the United States, with 5,000 to 7,000 deaths. The high incidence among infants under one year, and the high mortality rate in this group are especially striking. The late sequelae in this disease have been infrequently described in the literature, although they occur in a large number of the patients.

A great variety of cerebral complications in pertussis have been described. Clinical findings have included convulsions, monoplegia, hemiplegia, diplegia, paraplegia, deafness, blindness, aphasia and idiocy. Pathologically, meningeal and cerebral hemorrhages, meningitis, encephalitis, and thrombosis of cerebral veins and cerebral sinuses have been observed. Reports of some of these complications or sequelae have been frequently published; others, because of their rare occurrence, have been infrequently mentioned in the literature.

The purpose of this paper is to present an analysis of forty-seven cases of clinical cerebral complications which occurred in 6,002 patients with pertussis admitted to the Kingston Avenue Hospital for Communicable Diseases from 1932 to 1946 inclusive.

INCIDENCE

The incidence of cerebral complications in pertussis cannot be definitely established since not all patients with pertussis in a community are hospitalized. A review of the literature would also make it impossible to attempt such an estimate. For example, Valentine[1] reviewed the records of eighty-three cases of pertussis reported between the years 1880 and 1900 and found that sixty-four of the patients had convulsions during their illness. Of these sixty-four patients, fourteen died, twenty-two developed spastic paralysis, and twenty-eight showed residual neurological disturbances—a very high incidence as compared to the experiences of others.

Bazan and Maggi[2] reported fifteen cases of encephalitis in 600 cases of pertussis observed during a five-year period, an incidence of 2.5 per cent. Most of these cases of encephalitis occurred in the first two years of life. Vor dem Esche[3] reported 1,115 patients with pertussis seen during a two-year period.

From the Kingston Avenue Hospital for Communicable Diseases, Brooklyn.

TABLE I. INCIDENCE OF CEREBRAL COMPLICATIONS IN PERTUSSIS AND PERCENTAGE MORTALITY AS REPORTED BY VARIOUS OBSERVERS

AUTHOR	YEAR	NO. CASES PERTUSSIS	NO. CASES WITH CEREBRAL COMPLICATIONS	NO. DEATHS FROM CEREBRAL COMPLICATIONS	PER CENT MORTALITY
1. Valentine, P.	1890	83	64	14	22
2. Husler, J., and Spatz, H.	1924	?	?	?	72
3. vor dem Esche, C.	1931	1,115	172	103	60
4. Ley, R. A., and Dagnelie, J.	1932	135	8	7	86
5. Grenet, H., and Mourrut, E.	1933	238	22	20	87
6. Ellison, J. B.	1934	?	72	46	63
7. Habel, K., and Lucchesi, P.	1938	516	41	32	78
8. Bazan, F., and Maggi, R.	1940	600	15	12	80
9. Litvak, A. M., et al.	1932-1946	6,002	47	19	40

Of these, 172 showed cerebral symptoms, an incidence of 14 per cent. (See Table I.)

Hospital admissions of pertussis patients represent but a small percentage of the total number of cases and comprise the seriously ill and those with inadequate facilities for home care. On the other hand, convulsions in the course of pertussis may indicate the onset of complications such as bronchopneumonia, otitis media, tuberculosis, tetany, alkalosis, apnea, spasm of the glottis with anoxemia, and pneumothorax. Considerable care was exercised in this study to eliminate the patients with transient convulsive seizures which might have been due to the complications just mentioned. Thus, of a total of 6,002 hospitalized patients with pertussis at the Kingston Avenue Hospital, there were forty-seven patients with cerebral complications in a fifteen-year period, an incidence of 0.8 per cent. There were no significant dramatic variations from year to year in the number of cerebral complications. The general mortality rate from 1932 to 1938 inclusive was 9.4 per cent (Table II), while the general mortality rate from 1939 to 1946 was 3.3 per cent (Table III). This dramatic drop in the mortality rate was due to the use of sulfa drugs, hyperimmune human serum, and penicillin. The mortality rate in patients with cerebral complications of pertussis, however, has not been materially changed by these therapeutic agents.

TABLE II. ANALYSIS OF PERTUSSIS PATIENTS ADMITTED TO THE KINGSTON AVENUE HOSPITAL FROM 1932 TO 1938 INCLUSIVE

YEAR	PERTUSSIS PATIENTS	NO. DEATHS	PER CENT MORTALITY	PATIENTS WITH CLINICAL CEREBRAL COMPLICATIONS	NO. DEATHS
1932	403	45	11.2	1	0
1933	336	48	14.3	3	1
1934	430	32	7.4	1	1
1935	493	56	11.4	2	1
1936	229	17	7.4	8	2
1937	217	14	6.4	6	0
1938	650	49	7.7	3	1
Total	2,758	261	9.4	24	6

TABLE III. ANALYSIS OF PERTUSSIS PATIENTS ADMITTED TO THE KINGSTON AVENUE HOSPITAL FROM 1939 TO 1946 INCLUSIVE

YEAR	PERTUSSIS PATIENTS	NO. DEATHS	PER CENT MORTALITY	PATIENTS WITH CLINICAL CEREBRAL COMPLICATIONS	NO. DEATHS
1939	293	9	3.1	7	3
1940	346	16	4.0	6	4
1941	487	9	3.9	3	1
1942	645	22	3.4	1	1
1943	452	13	2.9	2	1
1944	285	12	4.2	2	2
1945	505	13	2.6	1	0
1946	231	5	2.1	1	1
Total	3,244	109	3.3	23	13

In this country about 200,000 cases of pertussis occur each year, with an average mortality rate of 3 per cent. When the disease is complicated by cerebral symptoms, the mortality rate rises abruptly. For example, the death rate in the series reported by Valentine[1] was 22 per cent. Husler and Spatz[4] reported a mortality rate of 72 per cent; Grenet and Mourrut[5] reported twenty-four cases complicated by convulsions, with a mortality rate of 87.5 per cent; vor dem Esche[3] reported a mortality rate of 60 per cent in 172 cases; Habel and Lucchesi[6] reported forty-one cases and found that the general mortality rate of 5 or 10 per cent for all hospitalized patients with pertussis uncomplicated by convulsions rose to 60 per cent when convulsions complicated the disease. Ley and Dagnelie[7] reported a mortality rate of 86 per cent. The average mortality rate for whooping cough in our series of 6,002 cases was 6.1 per cent. However, in the presence of cerebral complications, the mortality rate rose to 40.4 per cent.

LABORATORY DATA

Spinal fluid studies were done in thirty-eight of the forty-seven patients, and the fluid was found to be clear in every instance. The sugar content was normal except for two recordings of 166 and 160 mg. per cent. All fluids were sterile on culture and no organisms were seen in smears. Only seven of the specimens examined had a cell count over fifteen, the highest being 100 per cubic centimeter. The cells were almost always of the lymphocytic variety. There was no parallelism between the pleocytosis and the increase in the protein level, which varied from 18 to 120 mg. per 100 c.c. There was no correlation between the cell count of the spinal fluid, the severity of the complication, and the outcome in the individual patient.

The white blood cell count varied from 8,250 to 68,000 with the percentage of lymphocytes varying from 42 to 87 per cent. Similarly, there was no correlation between the severity of the complication, the prognosis of the individual case, and the total white count.

TEMPERATURE

The onset of cerebral complications in pertussis was almost always accompanied by a rise in the temperature. All but seven of the patients had an elevation of temperature ranging from 100 to 105° F.

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SEX

It has been pointed out by other observers that the incidence of cerebral complications in pertussis is higher in female than in male patients. Our studies substantiated these observations. Of the forty-seven patients with pertussis associated with cerebral complications, twenty-seven were female and twenty male. The fatality rate was nearly equally divided between male and female patients. We have no explanation to offer for the higher incidence of cerebral complications in female subjects. However, vor dem Esche,[3] in his series of 172 cases, found the sexes to be equally divided. Cruickshank[8] also remarked about the greater incidence of cerebral complications among female patients.

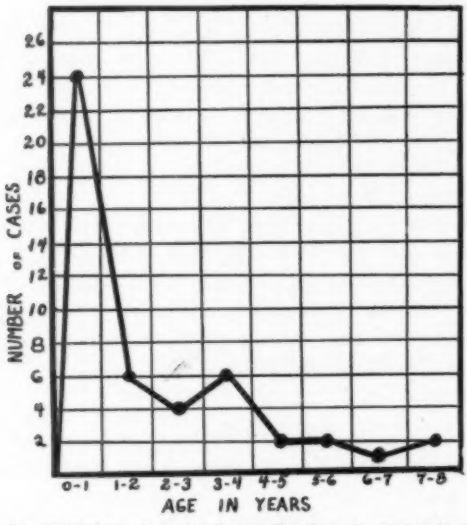

Chart I. Age incidence of cerebral complications in pertussis (47 cases).

AGE

It should be noted that in our series 50 per cent of the patients who developed cerebral complications were under one year of age, 60 per cent under 2 years (Chart I). Of forty-one patients reported by Habel and Lucchesi,[6] 75 per cent were under the age of one year. Zischinsky,[9] in a report of 12,577 cases of pertussis, found 83 per cent to be in infants 2 years of age and under, but unfortunately says nothing about the incidence of cerebral complications in this group.

Over a ten-year period from 1937 to 1946 inclusive, 4,111 patients with pertussis were admitted to the Kingston Avenue Hospital. Of these, 172 died. Of the total number of patients, 1,406 were infants under one year of age. One hundred twenty-six of these died. In other words, 73 per cent of the deaths that occurred during this ten-year period occurred in infants under one year of age. (Table IV.)

TABLE IV. ANALYSIS OF PERTUSSIS CASES AND DEATHS WITH PARTICULAR REFERENCE TO INFANTS UNDER ONE YEAR OF AGE

	YEAR										
	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	TOTAL
Total number patients	217	650	293	346	487	645	452	285	505	231	4,111
Total number infants under one year	43	202	99	101	134	263	158	124	178	104	1,406
Total number deaths	14	49	9	16	19	22	13	12	13	5	172
Total number deaths under one year	7	33	8	14	13	18	6	11	12	4	126

ONSET OF SYMPTOMS

Nelson[10] stated that cerebral complications in pertussis seldom appear during the catarrhal stage or even during the early part of the paroxysmal stage. He found that cerebral complications usually made their appearance at the peak of the paroxysmal stage and occasionally after it had begun to subside.

In our series it was noted that the onset of cerebral complications occurred during the third and fourth weeks of the disease in 72.5 per cent of the cases, while in the remaining 27.5 per cent the onset occurred in the first, second, fifth, and sixth weeks (Table V).

TABLE V. ONSET OF CEREBRAL COMPLICATIONS IN PERTUSSIS WITH REFERENCE TO STAGE OF THE DISEASE

STAGE OF DISEASE	NO. CASES
1st week	2
2nd week	6
3rd week	18
4th week	13
5th week	7
6th week	1
Total	47

ETIOLOGY

Numerous theories have been advanced regarding the etiology of cerebral complications in pertussis. Among the most recently advanced theories are those enumerated by Ellison:[11]

1. *Hemorrhage.*—This theory assumes that the nervous manifestations are due to gross mechanical interference with the circulation of blood in the brain due to the violence of the cough. The early authors such as Rhein,[12] Loschner,[13] and Smith[14] considered hemorrhages as the causative factor. West[15] and Luce[16] have reported cases in which, at autopsy, were found minute hemorrhages, edema, and cellular degeneration in the brain. Hockinjos[17] reported forty-two patients with post-mortem findings in some cases. The chief findings were minute hemorrhages in various parts of the brain, but he felt these to be insufficient to account for the outcome. Hockenbach[18] reported twenty-three cases in which a clinical diagnosis of brain hemorrhage had been made. There were nine post-mortem examinations of which five showed hemorrhages into the gray matter, two showed hemorrhages into the cortex, and two showed hemorrhages between the pons and dura. Cannelli[19] reported two deaths and suggested that minute hemorrhages had occurred either as a result of the action

of carbon dioxide on the vessels during the asphyxia due to a paroxysm or because of increased intraventricular pressure. Gross hemorrhages have been reported by Cabot.[20]

Ford[21] stated that until recent years it was customary to attribute the cerebral symptoms to hemorrhages, but many observers have noted that hemorrhages are sometimes absent or when present are not always extensive enough to explain the symptoms. He does not believe that hemorrhages alone, gross or microscopic, are responsible for the various cerebral complications.

Litvak[22] reviewed the reports of seventeen cases of pertussis in which visual disturbances occurred. He attributed these in some cases to hemorrhages into the internal capsule, and in others to retrobulbar neuritis.

2. *Spasmophilia.*—Powers'[23] report of five patients suffering from rickets and pertussis gave fresh impetus to this theory. His work was subsequently repeated by others. Askin and Zimmerman[24] and Litvak[22] reported normal calcium-phosphorus relationships in their patients, and Regan and Tolstoouhov[25] reported normal calcium levels on fifty-eight patients. However, the blood phosphorus was consistently below normal in 211 determinations. Trambusti and Sertori[26] did serum calcium determinations in eleven uncomplicated cases and found an average value of 8 mg. per 100 c.c. in the early stages of the disease. One 5½-month-old baby with clinical signs of tetany had a calcium level of 2.4 mg., but no convulsions were observed. The only other author to report convulsions due to low calcium levels was Bluhdorn.[27]

3. *Meningoencephalitis.*—This theory postulates the action of some biologic agent on the central nervous system, or the action of a toxin released in the respiratory tract by the Bordet-Gengou bacillus which may produce inflammatory changes in the brain. Criticism of this theory is based chiefly upon the lack of consistency in the pathologic changes and the fact that no biologic agent or toxin has been identified. However, many authors report their cases as "encephalitis," such as Askin and Zimmerman,[24] who base their opinions on the finding of diffuse scattered focal collections of small, deeply staining mononuclear cells, and occasional mononuclear cells with large, pale, vesicular nuclei and abundant cytoplasm present in these cellular foci. Singer[28] reported six cases in which there was a diffuse "hemorrhagic encephalitis," and he differentiates whooping cough encephalitis from other forms of encephalitis by the marked tendency toward diffuse microscopic hemorrhages. Hada[29] reported a patient with acute encephalitic changes in parts of the brain adjacent to a profuse exudate in the sulci. Husler and Spatz[4] demonstrated irreversible degenerative changes in the cortex, dentate nucleus, and corpus striatum without hemorrhage in two patients dying of pertussis complicated by convulsions. They describe a typical regressive change in the nerve cells of the cortex with loss of the staining properties of the cell except the nucleus. This suggested to them an encephalitic basis for the disease. Neuberger[30] described similar lesions in two patients but suggested that the changes were due to ischemic necrosis resulting from air emboli. Jochims[31] reported similar findings in a case and suggested the term "whooping cough encephalopathy." Strauss,

Rabiner, and Ginsburg[32] place whooping cough encephalitis in the class of demyelinating diseases of unknown origin, together with measles, smallpox, mumps, and other varieties of encephalitis.

4. *Neurotoxin.*—This theory assumes the presence of a toxin with a specific action on the central nervous system. The principal criticism directed against this theory is that the Bordet-Gengou bacillus does not produce an exotoxin. Mikulowski[33] also advanced the theory that the blood contained a toxin capable of affecting the tissues of the central nervous system and the endothelial lining of the vessels of the brain.

5. *Angiospasm.*—This theory, first advocated by Spielmeyer (cited by Ellison[11]), assumes the presence of a reflex mechanism due to functional disturbances of the circulation caused by repeated violent alterations in pressure produced by spasms of coughing. Canelli[19] reported two deaths and suggested that minute hemorrhages had occurred either as a result of the action of carbon dioxide on the vessels during the asphyxia of a paroxysm or because of increased intraventricular pressure. Yamaoka[34] reported three cases and suggested that angiospasm of the cerebral vessels bore a close relationship to the occurrence of convulsions.

According to Richer,[35] functional disturbances of the blood supply lead to lesions of the nervous tissue of a severity as great as one has been accustomed to attribute only to organic circulatory disorders, as in thrombosis and embolism.

Hiller and Grinker[36] report a case of a 3-year-old girl in whom the essential changes in the brain corresponded to softenings typically found associated with vascular occlusions. The striking observation was the tremendous dilatation of the cortical blood vessels within the softened areas, and their normal caliber in normal cortical areas. This is identical with what the authors found in carbon monoxide poisoning, and they feel that this is good evidence for stasis being the basis of the tissue damage. They go on to state that stasis in their case of pertussis could be objectively demonstrated, but that the reason for the development of this stasis was not obvious unless it was due, as in carbon monoxide poisoning, to the action of a circulating noxious agent on the vessel wall.

6. *Other Theories.*—Other theories have occasionally been mentioned in the literature. Thus, Hiller and Grinker discuss air embolism as a causative factor in the production of the cerebral manifestations. Neuberger[30] reported two cases and suggested that the changes were due to ischemic necrosis resulting from air emboli. Other authors have mentioned the similarity of the brain changes in pertussis with cerebral complications to those found in a woman dying of convulsions after coal gas poisoning.

It seems that the term pertussis encephalopathy, proposed by Jochims,[31] covers most adequately these conceptions and, in the present state of our knowledge concerning the pathogenesis of central nervous system lesions in pertusssis, should be the term of choice for the cerebral manifestations of the disease.

Of interest is the experimental work of Nakamura,[37] in which he attempts to demonstrate the significance of an exotoxin ("ausscheidende losliche toxin") of *Bacillus pertussis* as the causative agent in the production of meningoenceph-

alitis in rabbits. The same author reported that he was able to produce meningoencephalitis in rabbits with pertussis bacteria by damaging the liver function and elevating the temperature artificially.

Fonteyne and Dagnelie[38] caused convulsions and histologic changes similar to those found in human patients by injecting the endotoxin of *Hemophilus pertussis* intracerebrally and intrathecally into guinea pigs. Habel and Lucchesi[6] state that convulsions occur in the spasmodic stage when paroxysms are severe. This, they reason, results in venous congestion of the head and neck with severe anoxemia. Most of the convulsive movements involve many groups of muscles, and localizing neurological signs are absent, supporting the theory of a generalized chemical or mechanical change in the brain. They claim that the immediate cause of death appears to be a generalized vasomotor collapse, probably due to the effect of cerebral anoxemia. However, they state, certain patients have a definite encephalitis as the underlying cause since convulsions do occur when paroxysms are mild and in the absence of other infections such as bronchopneumonia, as evidenced by the perivascular round cell infiltration.

With so many theories from which to choose, it is probable that no one completely answers all the questions of pathogenesis. We have been unable to observe pathologic pictures that would lend support to the "encephalitic" theory. Signs of central nervous system inflammatory disease have been conspicuous by their absence. It is our feeling that perhaps where such findings as perivascular or slight meningeal infiltrations have been found, these may very well have been the result of a concomitant and unsuspected viral disease.

On the other hand, the paroxysms of whooping cough are very real and dramatic. Peripheral cyanosis indicates vividly the types of vascular changes which may be taking place in the central nervous system. Petechiasis is a common visceral finding in anoxemia irrespective of the cause. With marked alterations in blood flow in the brain incident to paroxysms of coughing, it is not difficult to understand why petechial hemorrhages are such a frequent finding in pertussis. When the vessels are sufficiently weakened, massive hemorrhage may be the result of rhexis of these channels.

Summary of the Etiological Factors Responsible for the Cerebral Complications in Pertussis (Advanced by Various Authors).—

1. *Vascular:*
   a. Hemorrhages
      1. Mechanical } Gross, microscopic
      2. Toxins } Meningeal, cerebral, subarachnoid
   b. Angiospasm and ischemia, resulting in nutritional death of brain cells
   c. Anoxemia
   d. Edema and congestion of the brain and meninges
2. *Inflammatory:*
   a. Virus, activated by the disease
   b. Bacterial
3. *Air emboli,* due to ruptured alveoli
4. *Tetany*

CLINICAL PICTURE

It is well to bear in mind that concomitant nonrelated pathologic findings may complicate the clinical picture in patients with cerebral manifestations in pertussis. We have encountered in our series five such cases. In one a glioma of the brain was found on post-mortem examination, and in four, bacterial meningitis was demonstrated. These cases were excluded from this report.

The clinical pattern of cerebral complications in pertussis is as follows:

1. Convulsions and coma:
   a. Continuous or recurrent
   b. Generalized or focal
   c. Child may die in the attack.
   d. Child may survive to become stuporous.
   e. Coma may persist for days or weeks.
2. Paralyses:
   a. Cerebral type:
      1. Motor: monoplegia, diplegia, hemiplegia, paraplegia
      2. Sensory: aphasia, deafness, and blindness
   b. Spinal type:
      1. Spastic
      2. Flaccid
3. Meningeal syndrome
4. Neurological signs
5. Peripheral neuritis
6. Mental changes
7. Epilepsy

The most frequent symptoms at the onset in the cases studied were a rise in the temperature and an abrupt convulsion which was continuous or recurrent after a short pause. In most of the cases the onset of the convulsions was in the third or fourth week of the disease. These convulsions as a rule were generalized, but occasionally they were focal in character. The child may die in the attack, or survive to become listless, drowsy, and stuporous. The stupor or drowsiness may persist for days or weeks. Various neurological signs may manifest themselves during this time. Monoplegia, diplegia, hemiplegia, hyperreflexia, hyperspasticity, twitchings of muscles, and rigidity of various degrees may be found. Brudzinski, Kernig, and Babinski signs are almost always elicited. The pupils are frequently dilated and unequal, and hemorrhages in the eye grounds are found not infrequently. Temporary amaurosis and loss of speech were observed and recorded in the literature by one of us (A. M. L.). Bulbar palsies are occasionally encountered. The patients are unable to swallow, cannot hold up the head, mucus accumulates in the throat, and they cannot speak. Removal of the mucus by suction, and a high Trendelenburg position for postural drainage, continuous intravenous fluids of normal saline and glucose, and gavage feedings are essential in the care of such patients.

Some of these patients regain consciousness in a few days and recover without sequelae, while others may remain in stupor for weeks and regain consciousness slowly. Some of these die from intercurrent infections; others survive to develop sequelae.

TABLE VI. FREQUENCY OF SIGNS AND SYMPTOMS IN THE FORTY-SEVEN PATIENTS WITH CLINICAL CEREBRAL COMPLICATIONS IN PERTUSSIS

SIGNS AND SYMPTOMS	NUMBER OF TIMES FOUND
Convulsions	37
Stupor	14
Weakness of extremities	12
Hyperactive tendon reflexes	9
Nuchal rigidity	9
Cranial nerve involvement	8
Absent reflexes	7
Positive Babinski sign	6
Spasticity of extremities	5
Hemiplegia	4
Opisthotonos	4
Coma	4
Hypoactive tendon reflexes	3
Difficulty in speaking	3
Twitching of extremities	3
Papilledema	3
Blindness	3
Nystagmus	2
Strabismus	2
Difficulty in swallowing	2

PROGNOSIS

In our series of forty-seven cases there were nineteen deaths. The mortality rate was highest among children below 2 years of age (60 per cent). In this connection it must be remembered that the incidence of cerebral complications is highest in that particular age bracket, and accordingly one would expect a higher proportionate mortality. The general mortality rate in our series of cases was 40.4 per cent. In general, it may be stated that one-third of the patients with cerebral complications die in the acute phase; one-third recover to develop sequelae; and one-third recover completely. This coincides with the opinion of other observers.

SEQUELAE

In general, it would appear that the prognosis for a complete cure in whooping cough complicated by cerebral manifestations is not favorable. Thus, Eley[39] reported fourteen cases in eleven of which there were permanent injuries to the central nervous system, either in the form of mental retardation, paralysis, recurrent convulsions, or various combinations of these. In our series, mental retardation, paralysis, loss of visual acuity, and ataxia were noted. By far the greater proportion of our recovered patients were discharged from the hospital without apparent sequelae. Several authors have shown that the effects of pertussis encephalopathy may manifest themselves many years after apparent recovery. Eley[39] in 1930 reported four such patients, in whom the symptoms became manifest years after the attack of pertussis.

Among the more frequently reported sequelae are personality and behavior changes. In a very interesting paper, Lurie and Levy[40] report a study of 243 children who had pertussis. Summary of their findings is as follows:

1. Five hundred children were studied in the Child Guidance Home, Cincinnati.

2. Two hundred and forty-three of these children had had whooping cough in the past.

3. Fifty-eight children had whooping cough at ages between 3 weeks and 2 years.

4. Thirty-four of these presented a definite relationship between neurological sequelae and behavior disorders and personality changes which occurred between 4⅓ years and 17⅓ years of age.

5. The following difficulties were noted:

a. General behavior problems	21
b. School maladjustment	8
c. General nervousness	5
d. Delay in onset of walking and talking	16
e. Convulsive seizures	9
f. Endocrine disturbances	9
g. Neuropathologic sequelae	25
h. Nerve deafness	15
i. Speech disorders	9
j. Abnormal electroencephalograms	5
k. Cortical atrophy on pneumoencephalograms	6

Two of the children had superior intelligence; eight were average; nine were subnormal; five were borderline; and two were feeble-minded. As for behavior changes, some were prepsychotic and some psychotic. Some had paranoid tendencies and visual and auditory hallucinations. Others had no interest in their appearance.

On the whole, the children studied fell into the following groups: Eight children were prepsychotic or psychotic; six children showed progressive intellectual deterioration; seventeen showed postencephalitic type of behavior with extreme motor restlessness, impulsiveness with a tendency to destructive activity and unpredictable behavior. Only a few of these showed intellectual retardation. Three of the children showed a type of behavior that was a combination of two or more of the preceding.

It is of interest to speculate whether personality and behavior changes may, in part at least, be due to cerebral atrophy following pertussis. That such cerebral atrophy does occur has been shown by Ford[21] on post-mortem examination and also by Eley[41] on pneumoencephalographic studies on his patients. Figs. 1 and 2 are reproduced from his article.* In Fig. 1, dilatation of the ventricular system is demonstrated, and in Fig. 2, cerebral atrophy, the most common sequela in cerebral complications of pertussis.

Visual disturbances, either temporary or permanent, may occur, and Litvak[22] collected seventeen such cases and added one of his own. Among

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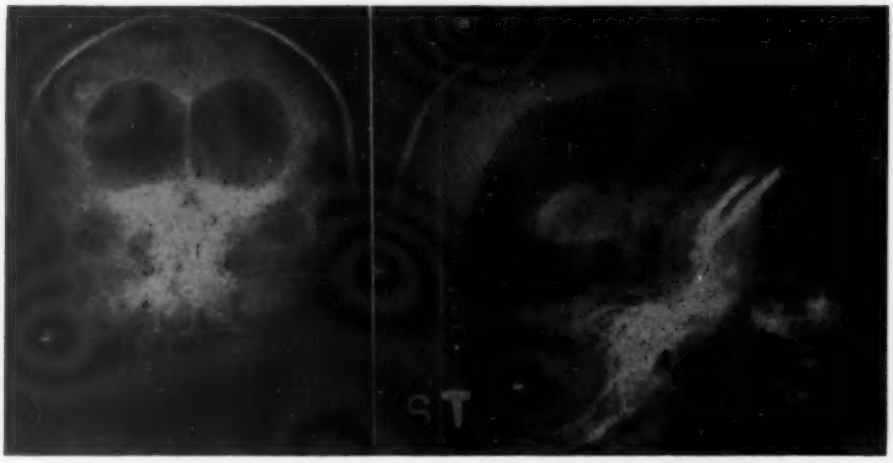

Fig. 1.—Patient admitted at the age of 4½ years, for recurrent convulsions. Had a severe attack of whooping cough at the age of one year and convulsions at that time. Child showed opisthotonic position and generalized spasticity, was mentally retarded, and had a right-sided hemiplegia. Note the dilated ventricles bilaterally.

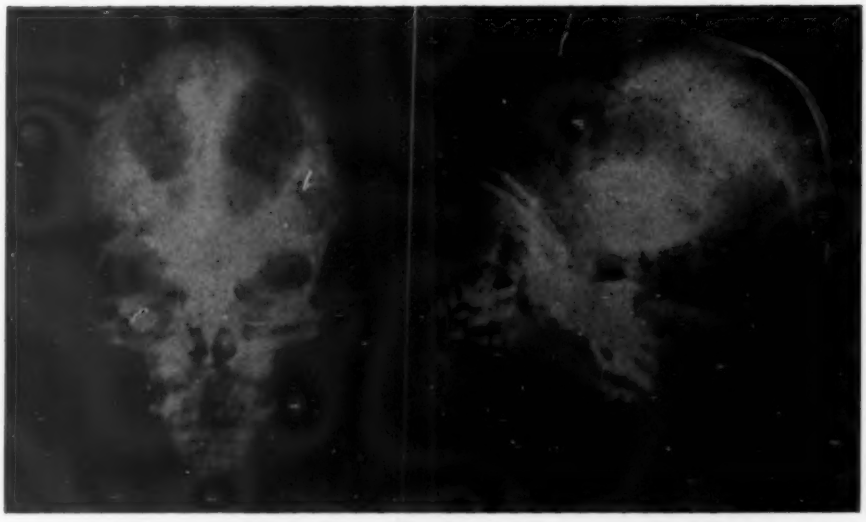

Fig. 2.—Child 19 months old, admitted because of inability to move left arm, left leg, and right arm. The patient had whooping cough at the age of one month. During the course of whooping cough she developed bilateral internal strabismus. One month prior to admission she became drowsy and was unable to use her left arm, left leg, and right arm. She did not recognize her parents and remained semistuperous. There was an old choroiditis in the eye grounds and the discs were blurred. Note the large, dilated, asymmetrical ventricles and cerebral atrophy.

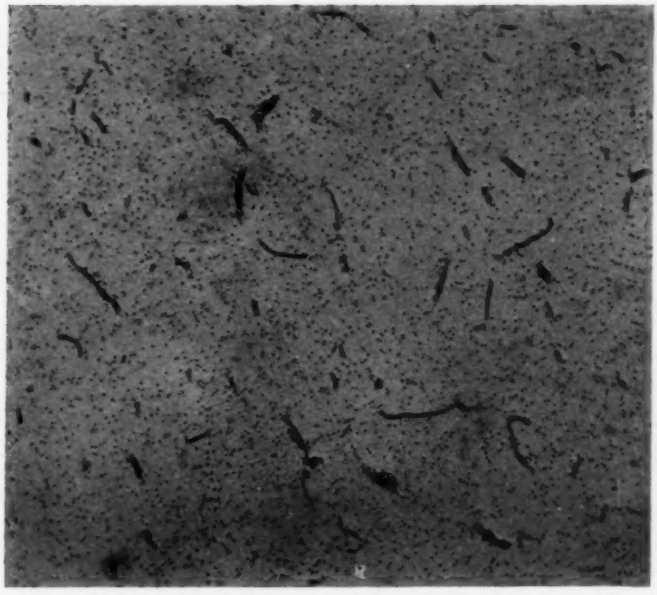

Fig. 3.—Pertussis. Marked congestion of vessels. (Hematoxylin and eosin stain, ×80.)

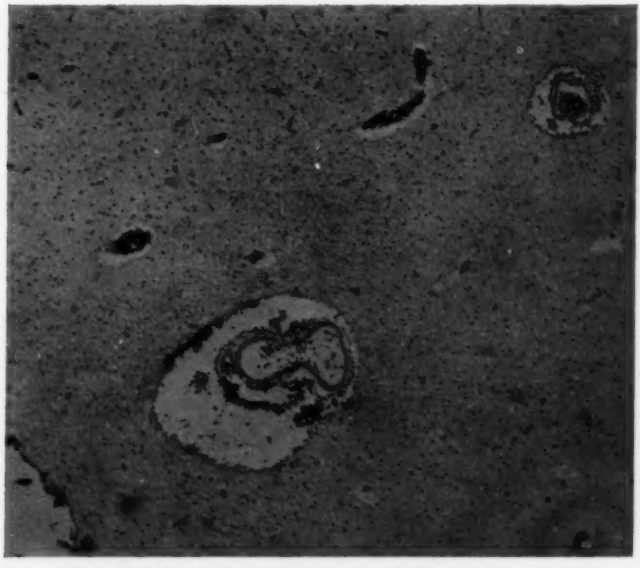

Fig. 4.—Section of brain showing hemorrhage into Virchow-Robin's space. (Hematoxylin and eosin stain, ×80.)

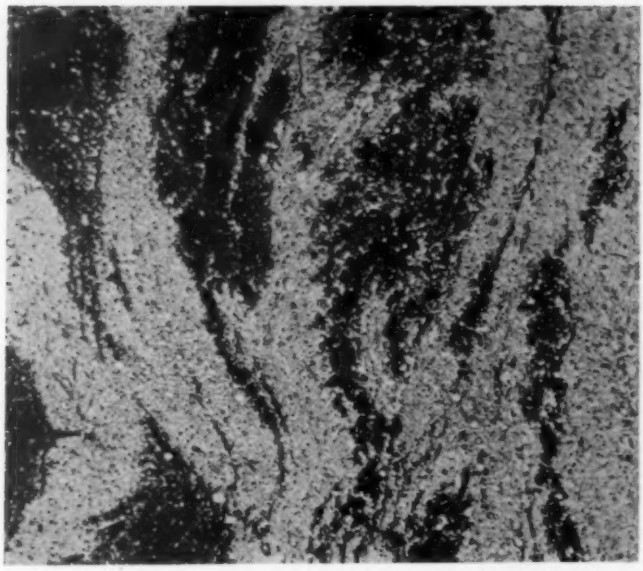

Fig. 5.—Section of brain showing diffuse hemorrhage. (Hematoxylin and eosin stain, ×80.)

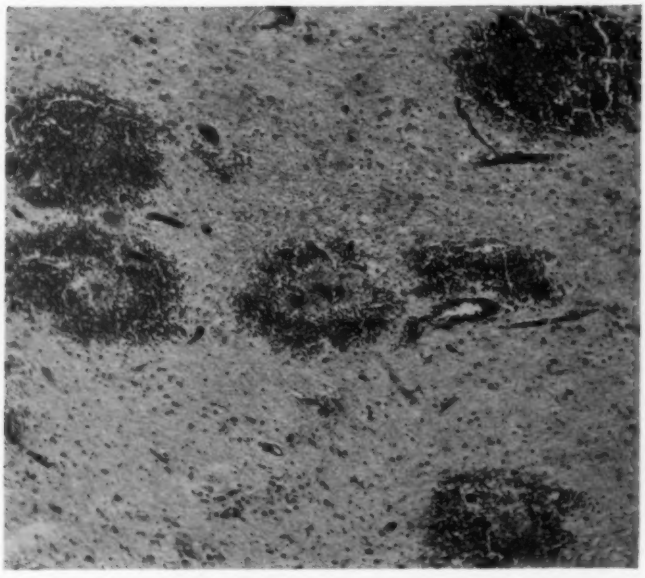

Fig. 6.—Section of brain showing thrombi in small vessels which are surrounded by extravasated blood. (Hematoxylin and eosin stain, ×80.)

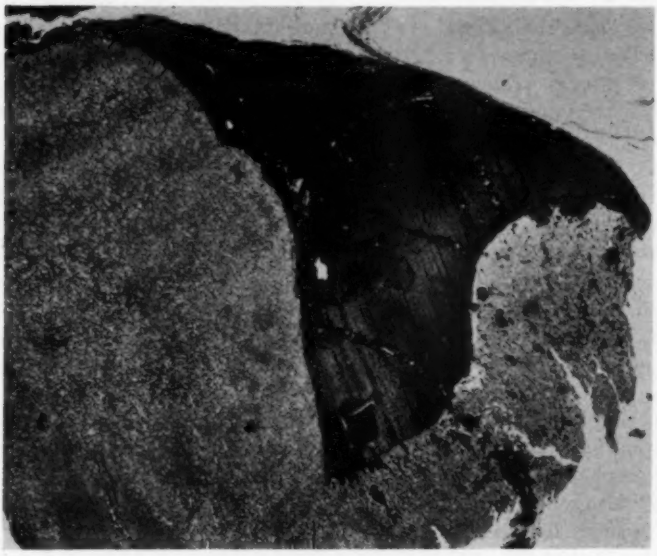

Fig. 7.—Section of brain showing massive subarachnoid hemorrhage. (Hematoxylin and eosin stain, ×80.)

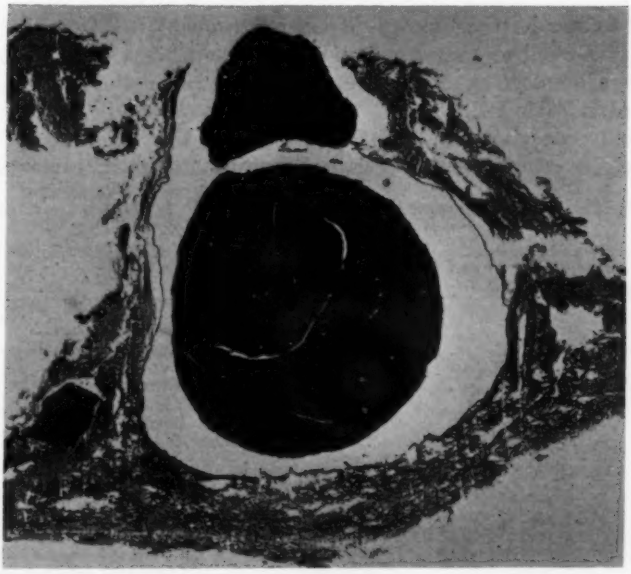

Fig. 8.—Section of brain showing thrombus in superior saggital sinus of dura. (Hematoxylin and eosin stain, ×80.)

these patients, two were permanently blind, thirteen had transitory blindness, and in two cases the ultimate results were unknown. Eley[41] added two cases of visual disturbances after pertussis. Lazarus and Levine[42] also reported a case of blindness. They felt that cerebral edema or acute hemorrhagic encephalitis accounts for the ocular changes in the majority of cases.

Sears[43] reported a case of right-sided hemiplegia, with eventual complete recovery. A case of hemiplegia was also reported by Cabot.[20] It is of interest to note that right-sided hemiplegia occurs more often than left, but the mortality rate seems to be higher in left-sided hemiplegia. Valentine[1] reported hemiplegia as occurring on the right side in twenty patients, of whom one died, whereas left-sided hemiplegia occurred in fourteen of his cases, with eight deaths. Grant and Williams[44] reported a case of left-sided hemiplegia and emphysema of the chest, neck, and cheeks. One year later, encephalography revealed gross atrophy of the right cerebral hemisphere with enlargement of the right lateral ventricle.

Cerebellar ataxia was reported by Kokken,[45] who states that this is a rare complication and that only four such cases have been reported. Hydrocephalus and macrocephalia were reported in one case by Camauer.[46]

Eley[41] also reported dilatation of the ventricles, diffuse cerebral atrophy, and calcified hemorrhages in a series of patients. Epilepsy as a sequela was reported by Worster-Drought.[47] This patient had pertussis at the age of 5 years. The epileptic seizures started five years after the original illness, and at the age of 16 years he still had epileptiform attacks.

FOLLOW-UP STUDIES

To date, we have succeeded in tracing twelve patients. The follow-up consisted of a detailed history regarding character, behavior, mental, physical, and social changes, if any, and a careful physical examination. The findings are summarized in Table VII.

The only conclusion that can be drawn from this follow-up series is that if pertussis is complicated by cerebral manifestations, it leaves the central

TABLE VII. FOLLOW-UP STUDIES ON TWELVE PATIENTS WHO HAD CEREBRAL COMPLICATIONS DURING WHOOPING COUGH

AGE AT TIME OF ILLNESS	AGE AT TIME OF FOLLOW-UP	INTERVAL SINCE ILLNESS	FINDINGS
7 weeks	3 years	2½ years	Normal
4 months	7 years	6 years, 8 months	Normal
5½ months	15½ months	10 months	Died of encephalitis of unknown etiology
7 months	20 months	13 months	Normal
8 months	6½ years	5 years, 10 months	Normal
1 year	4 years	3 years	Normal
14 months	4 years	2 years, 10 months	Repeated convulsions with every subsequent illness, no matter how mild
16 months	8 years	6 years, 8 months	Very "nervous"
3 years	13 years	10 years	Normal
3 years	3 years, 1 month	5 months	Ataxia
6 years	6 years, 2 months	2 months	Bilateral secondary optic atrophy
6½ years	15 years	8½ years	Petit mal seizures for five years after whooping cough

nervous system vulnerable to further injury. Thus, three of our twelve follow-up patients showed further convulsive episodes.

One patient remained normal for a period of ten months, then suddenly developed convulsions for which she was hospitalized at another institution. She died the day following admission. The diagnosis on the post-mortem findings was acute encephalitis of unknown origin.

One patient developed petit mal seizures following pertussis with cerebral complications. The attacks lasted for a period of five years, then suddenly ceased. He has been symptom-free for the past three and one-half years, attends high school, is a good student and a star basketball player.

Another child, now 4 years of age, has had repeated convulsive seizures with each subsequent illness. Thus, his measles was ushered in with a convulsion, he had an attack of bronchopneumonia complicated by convulsions, and each upper respiratory infection which has been accompanied by fever has also been accompanied by a convulsion.

A 3-year-old child developed ataxia which was of transient nature and showed considerable improvement after five months. One 6-year-old child, who became totally blind, gradually regained his vision, but when seen two months after discharge showed bilateral secondary optic atrophy.

One must remember that considerable time must elapse before the development of personality changes and behavior disorders appear.

Summary of Sequelae.—

1. Mental retardation
2. Various paralyses
3. Recurrent convulsions
4. Loss of visual acuity
5. Personality and behavior changes
6. Delay in walking and talking
7. Epilepsy
8. Idiocy
9. Blindness and deafness
10. Hemiplegia, diplegia, spastic paraplegia
11. Cerebellar ataxia
12. Hydrocephalus
13. Diffuse cerebral atrophy

PATHOLOGY

The pathologic changes occurring in the brain of patients with cerebral complications in pertussis are interrelated with the etiological factors causing these changes. Here, too, opinion is divided among pathologists as to whether the pathologic changes found in the brain are to be considered inflammatory, degenerative, toxic, or hemorrhagic.

Wechsler,[48] discussing the brain lesions in pertussis, states that in addition to the presence of an inflammatory reaction, the condition is also characterized by the predominance of hemorrhagic foci which are scattered throughout the cerebrum, the midbrain, in the region of the aqueduct, and in the pons and

medulla. Mikulowski[33] stated that the usual findings at autopsy are hyperemia, edema, congestion, and meningeal and venous thrombosis. Hiller and Grinker[36] in describing their patient state: "No thrombus or other organic obstruction to the vessels could be found, yet the essential pathology corresponds to the softening typically found associated with vascular occlusion. The type of lesion varied from ganglion cell 'Erbleichung' to incomplete and complete softening, which points to a slowly increasing diminution of the blood supply. Complete tissue death did not take place, as even the center of the focus revealed a proliferative ectodermal reaction. The striking observation was the tremendous dilatation of the cortical blood vessels within the softened area. This is identical with that which we find in carbon monoxide poisoning and speaks strongly for stasis as the basis of tissue damage." The autopsy findings in the case reported by Askin and Zimmerman[24] showed acute diffuse encephalitis and subarachnoid hemorrhages.

Canelli[19] is of the opinion that focal hemorrhages, cerebral or meningeal, are very rare in pertussis, and that in all cases one may observe encephalitic lesions with a triad of pathologic findings—that is, hemorrhagic foci with necrosis, perivascular demyelinization, and perivascular infiltration. Ford[21] reports a case of a child, aged 20 months, with pertussis who developed cerebral diplegia. At autopsy there was found a great loss of cortical nerve cells unrelated to vascular disturbances or inflammatory processes.

Dolgopol,[49] after a careful analysis of fifteen autopsied patients at the Willard Parker Hospital, New York, sums up her findings as follows: "The changes in the brain in pertussis are apparently noninfectious. They are most likely of circulatory origin and consist of edema, ischemic cellular degeneration, multiple hemorrhages (usually small) and lymphocytic plugs in veins and capillaries. On rare occasions a 'secondary encephalitic' reaction may be observed in addition to the aforementioned changes."

Ford[21] studied eleven patients with cerebral complications in pertussis. Ten of these patients died within a few days of the onset of the cerebral complications, and one lived several months. In one case he found a massive hemorrhage in the subarachnoid space; in three cases the cerebral vessels were intensely congested and innumerable minute hemorrhages were found scattered throughout the brain. He did not encounter softening or thrombosis and no inflammatory phenomena. Very little injury to the cortical cells or nerve fibers was noted. In one case in which the patient survived for six months there was general symmetrical wasting of the cortex which was most obvious in the frontal lobes.

In the course of this study, the brains of thirty-nine infants and children who died of pertussis were examined. Five of these were eliminated because post-mortem examination revealed a complicating meningitis in four patients and a glioma of the brain in one patient (Table VIII).

Gross examination in all instances showed congestion and edema, which was confirmed histologically. The cerebrospinal fluid was almost invariably increased in amount. Histologically, interfibrillary edema was often striking,

TABLE VIII. SUMMARY OF PATHOLOGIC MATERIAL STUDIED

MATERIAL	NUMBER
Pertussis patients on whom autopsy was performed	76
Brains examined	39
Brains excluded because of other complicating factors (Pneumococcic, streptococcic, tuberculous, and influenzal meningitis, and glioma of the brain)	5
Brains with pathologic changes due to pertussis	34
Brains with clinical diagnosis of pertussis encephalopathy	17

as was the marked capillarity of the brain. Dilatation of Virchow-Robin's space was often seen. These findings were not confined to any one area of the central nervous system.

Petechiasis, either gross or microscopic, was present in nineteen of the thirty-one cases. These punctate hemorrhages were variable in number, and were especially prominent in the pons, basal ganglia, and cerebrum. Often, the extravasation of blood was confined to Virchow-Robin's space, but in other instances, there was extension into the brain substance itself. Massive intracerebral hemorrhage was a rare finding, and subarachnoid hemorrhage was seen in only three instances. Thromboses were seen twice. In one case, there were multiple thrombi in small intracerebral capillaries and venules; in the other, there was a large thrombus obstructing the superior sagittal sinus of the dura mater. In some cases, small plugs composed of lymphoid cells were also noted. These were disregarded, however, because the effect of stasis and settling of blood in the cadaver could not be excluded as etiological factors in their production. (Table IX.)

TABLE IX. PATHOLOGIC CHANGES IN THE CENTRAL NERVOUS SYSTEM IN PERTUSSIS (34 CASES)

PATHOLOGIC CHANGE	NUMBER OF CASES
Congestion	34
Edema	34
Petechial hemorrhage	19
Subarachnoid hemorrhage	3
Thrombosis	2

At no time were perivascular or perineuronal collections of inflammatory cells seen. Infiltrations of the meninges, although carefully looked for, were also absent. These features are usually seen in association with infectious disease of the central nervous system. Their absence, therefore, was interpreted as indicating that the pathologic changes of the central nervous system in pertussis were largely the result of vascular phenomena rather than due to direct action on the brain of any toxin or actual bacterial invasion. The term "pertussis encephalopathy" is considered preferable to "encephalitis" for these reasons.

THERAPY

Therapy was essentially symptomatic, with sedatives, dehydrating measures, spinal punctures, transfusions, intravenous fluids, oxygen, human hyperimmune serum, sulfa drugs, penicillin, and ether and oil used as indicated. Avertin anesthesia was used in one case with apparent success. Various other therapeutic agents have been used and reported from time to time. Thus, Hyland,[50]

Cruickshank,[8] and others reported on the use of vaccine and convalescent serum. Neither appeared to be of benefit after the onset of the symptoms. The following is a summary of the therapeutic agents used by us in the treatment of the cerebral complications of pertussis:

1. Lumbar puncture
2. Sedatives: sodium phenobarbital, bromides, chloral hydrate
3. Ether 25 per cent in oil by rectum
4. Avertin anesthesia
5. Hypertonic glucose intravenously
6. Magnesium sulfate 50 per cent intramuscularly
7. Intravenous fluids
8. Transfusions
9. Oxygen tent
10. Human hyperimmune serum intramuscularly and intravenously
11. Gavage feedings
12. Sulfa drugs
13. Penicillin
14. Ascorbic acid
15. Calcium gluconate intravenously
16. Vitamin K

CASE REPORTS

A few typical case reports are presented:

CASE 1.—V. C., a white boy 6 years old, was admitted with a history of pertussis of three weeks' duration, complicated by pneumonia which had practically subsided at the time of admission. The day before admission the child developed a right facial paralysis and visual disturbances. Neurological examination showed a right supranuclear facial paralysis, scanning speech, normal reflexes, complete blindness with absent perception of light. There was weakness of the right arm and leg. The eye grounds showed a moderate bilateral papilledema. The remainder of the physical examination was negative. The temperature was 98.8° F. The spinal fluid was clear, pressure normal, protein 18 mg. per 100 c.c., globulin negative, sugar 55 mg. per 100 c.c., smear and culture negative, 2 cells both lymphocytes. The white blood count was 14,900 with 85 per cent lymphocytes. All other laboratory data were normal.

Two weeks after admission the child began to see light. The other symptoms gradually receded, although the vision remained impaired. Pallor of the optic discs, interpreted as secondary atrophy, became evident. The patient was discharged after five and one-half weeks, the only remaining symptom being markedly defective vision.

CASE 2.—B. K., a white female infant 3 years old, was admitted with a history of pertussis of four weeks' duration, and of bronchopneumonia of three days' duration. Examination revealed an acutely ill, prostrated child with signs of labored respirations and moderate cyanosis. The chest showed signs of bilateral bronchopneumonia. There were no other abnormalities noted. Temperature was 103° F., respirations 52. The spinal fluid was clear and under normal pressure. The cell count was 15, all lymphocytes, protein 60 mg., globulin negative, sugar normal, smear and culture negative. The blood white count was 33,600 with 81 per cent lymphocytes. Two or three days after admission the signs of cerebral involvement became manifest. There was constant aimless motion of the head and extremities, poor coordination of the eyes, sluggish reaction of the pupils, and diminished tendon reflexes. The eye grounds were normal.

The patient continued to run a stormy course with temperature ranging up to 104° F. The child was semicomatose and apparently completely blind and deaf. About one week after admission the chest began to clear and the child was removed from the oxygen tent. The pupils continued to react sluggishly, there was loss of control of the ocular muscles, and the reflexes remained hypoactive. Vomiting was marked. After three and one-half weeks, improvement was noticed. The child responded better to stimuli, the vomiting became less pronounced, the blindness and deafness improved. The child was seen again five months after discharge. At this time she was perfectly well except for a slight ataxia which later disappeared.

CASE 3.—I. L., a white girl, age 7 years, was admitted to the hospital with a history of pertussis of four weeks' duration and of four convulsions on the day of admission. Examination revealed an acutely ill, drowsy patient who responded to questioning. There was moderate nuchal rigidity and right supranuclear facial paralysis; the tongue deviated to the right; there was weakness of the right upper extremity, absent abdominal reflexes on the right side, bilateral Babinski signs, and hypoactive deep reflexes. The temperature was 102° F. The eye grounds were normal. The spinal fluid was clear, contained 5 cells, all lymphocytes, protein 40 mg., globulin negative, sugar normal, smear and culture negative. The white blood count was 20,700 with 65 per cent lymphocytes.

Intermittent convulsions continued for four days after admission. Weakness of the right lower extremity was noted. Because of the almost constant convulsions despite the usual sedatives, avertin therapy was instituted and continued for four days. This gave immediate and continued relief from the convulsions. There was continual gradual improvement, and the patient was discharged one month after admission without residual signs.

CASE 4.—A. W., white female infant, 10 months old, was admitted with a history of pertussis of two weeks' duration and of convulsions for twenty-four hours preceding admission. Examination revealed an acutely ill comatose infant. The extremities were flaccid. No other abnormalities were noted. The temperature was 102.2° F., pulse 150, respirations 40. The spinal fluid was clear, with pressure increased, and contained 10 cells, all lymphocytes; sugar was normal, smear and culture negative. The patient had several convulsions shortly after admission, but by the following day had regained consciousness. Convalescence was uneventful, and she was discharged two and one-half weeks after admission.

CASE 5.—W. B. W., male infant, age 8 months, was admitted to another hospital for diarrhea. During the course of treatment for the diarrhea a history of exposure to pertussis was obtained, questioning in this respect being prompted by the development of a croupy cough. The child was transferred to the Kingston Avenue Hospital. At the time of admission the temperature was 102.4° F.; the patient was dehydrated; the respirations were shallow and rapid. There were frequent paroxysms of cough followed by whooping. There was a transitory strabismus, nystagmus, and tremors of the left side of the body. Convulsions developed shortly after admission and remained continuous until the child died several hours after admission. The spinal fluid showed 4 cells, all lymphocytes.

CASE 6.—W. S., male infant, 7 months old, was admitted with a history of pertussis of two weeks' duration. He had a convulsion which lasted three minutes on the day of admission. On admission the child had a generalized convulsion which lasted six minutes. There were transitory strabismus and nystagmus. The spinal fluid was clear and contained 15 cells, all lymphocytes. The white blood count was 15,800 with 67 per cent lymphocytes. Convulsions continued on and off for the following eleven days in spite of therapy, and the child died on the eleventh hospital day.

SUMMARY

1. Over a period of fifteen years, 6,002 cases of pertussis were seen at the Kingston Avenue Hospital. Forty-seven of these were complicated by clinical cerebral manifestations.

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2. (a) During the years 1932 to 1938 inclusive, 2,758 patients were admitted and 261 died, a general mortality rate of 9.4 per cent. Twenty-four cases were associated with cerebral complications. Six patients died, a mortality rate of 25 per cent.

(b) From 1939 to 1946 inclusive, 3,244 patients were admitted and 109 died, a general mortality rate of 3.3 per cent. Twenty-three cases were complicated by cerebral manifestations and thirteen patients died, a mortality rate of 56.5 per cent.

3. Of the forty-seven patients with cerebral complications, 28 survived and nineteen died, an average mortality rate of 40.4 per cent.

4. The onset of cerebral complications was almost always accompanied by convulsions and a sudden rise in temperature.

5. Fifty per cent of the patients who developed cerebral complications were under one year of age, and 60 per cent were under 2 years of age.

6. In 72.5 per cent of the patients, the onset of the cerebral complications occurred during the third and fourth weeks of the disease.

7. Spinal fluid studies were made in thirty-eight of the forty-seven patients. The findings were normal in all but eight cases. There was no correlation between the prognosis for life or sequelae and the spinal fluid findings.

8. The prognosis in patients with cerebral complications in whooping cough depends upon the age of the patient, the severity of the paroxysm, the nutritional state of the patient, the length of the convulsive seizure, the duration of the coma, and upon the presence of an associated complication.

9. In round figures, one-third of the patients with cerebral complications die, one-third recover to develop sequelae, one-third recover completely.

10. Twelve of the twenty-eight surviving patients in our series were followed over periods ranging from two months to eight years. Five (43 per cent) of them showed a tendency to further central nervous system manifestations.

11. The pathologic changes in the brains of thirty-four autopsied patients with cerebral complications were edema and congestion of the brain, petechial hemorrhages, subarachnoid hemorrhages, and thrombosis of cerebral veins and sinuses.

12. No changes of an inflammatory nature were observed.

13. The pathologic changes may be considered due to vascular disturbances or degenerative changes incident to anoxemia rather than inflammatory in origin.

14. The term "encephalopathy" appropriately covers these pathologic changes.

15. Treatment is entirely symptomatic. There is no effective specific therapy.

16. Present trends in age distribution of pertussis indicate a greater incidence in infants under one year of age.

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PEDIATRIC DEATHS IN A LARGE GENERAL HOSPITAL

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THIS inventory was undertaken with the conviction that it would serve as a stimulus for improving the quality of care given to our patients; the present report only sets a tentative pattern for subsequent periodic analyses. The year 1942 was selected because well-known handicaps existing in most hospitals at that time might be expected to accentuate certain problems ordinarily encountered in any hospital which cares for infants and children. Eleven members of our present pediatric staff have cooperated in reviewing all records of 436 fatalities which occurred among 12,470 admissions to the three pediatric and children's surgical divisions of the Charity Hospital at New Orleans. The authors have referred many controversies which arose during these reviews and accept responsibility for all designations employed herein. This material was gathered primarily for intradepartmental purposes; because no attempt has been made to compare it with Federal, State, or other hospital statistics, we felt free to deviate from conventional methods for handling vital data. The inferior quality of some clinical and pathologic studies in that year of wartime shortages occasionally called for arbitrary retrospective interpretations and has undoubtedly influenced some of our conclusions.

With few exceptions, patients were indigent residents of Louisiana. Critical perusal of records justified the conclusion that, in the light of present medical knowledge, at least 209 (48 per cent) of all deaths could be classed as inevitable at the time of admission. Nine of these patients were dead on arrival, forty-one were moribund and expired during the first hour of hospitalization, and the other 159 were proved to have conditions with inherently hopeless prognoses. We considered that thirty-seven (9 per cent) of these deaths might have been prevented had correct diagnoses been recognized earlier and proper therapy carried out. No such decisions as to preventability could be made for the remaining 192 deaths.

I. DEATHS IN THE NEONATAL PERIOD OF HOSPITALIZATION

As noted in Tables I and II, records indicate that 34 per cent of all pediatric deaths, and 80 per cent of all deaths in the neonatal period of hospitalization, occurred among infants who weighed less than 2.5 kg. at birth and were classed as premature. These premature infants were usually kept in the nurseries until a weight of 2.75 kg. had been attained, whereas mature infants usually remained only about five days. The fatality rate among premature infants was twenty-nine times higher than that among mature infants. One premature birth was

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reported for every seven and one-half mature births; this ratio was significantly higher for Negroes (1:7.4) than for whites (1:7.9), and for female (1:6.7) than for male children (1:8.5). The total death rate for all infants for any duration of stay in delivery rooms or nurseries was 36.8 per 1,000 live births, 29.1 for premature infants, and 7.7 for those who weighed more than 2.5 kg. at birth. Adequate explanations for the high percentage of premature births and the high total death rate during the neonatal period of hospitalization will require a more detailed analysis of obstetric and medical causes than is possible at present. The causes we have listed re-emphasize the importance of antenatal and natal factors; only about 20 per cent of all neonatal deaths could be ascribed to causes developing after delivery.

TABLE I. DEATHS AMONG INFANTS AND CHILDREN IN CHARITY HOSPITAL AT NEW ORLEANS, 1942

	DEATHS	ADMISSIONS	DEATHS PER 100 ADMISSIONS	DEATHS AS PER CENT OF ALL DEATHS
All neonatal	187	5,084	3.68	43.0
Premature	148	596	24.83	34.0
Mature	39	4,488	0.87	9.0
All others	249	7,386	3.37	57.0
Total	436	12,470	3.49	100.0

TABLE II. DEATHS IN THE NEONATAL PERIOD

	PREMATURE	MATURE	TOTAL NEONATAL	RATIO PREMATURE: MATURE
Born alive	596	4,488	5,084	1.0:7.5
Died	148	39	187	3.8:1.0
Percentage of deaths in specified group	24.8	0.87	3.7	29.0:1.0
Deaths per 1,000 live births	29.1	7.7	36.8	3.8:1.0

A. DEATHS AMONG PREMATURE INFANTS

Of 596 premature infants, 24.8 per cent died; all but two were born in the hospital, and these were admitted during the first day of life. Interesting variations were encountered when these deaths were expressed according to color and sex (Tables III, IV). Seventy-six and three-tenths per cent of all premature infants born and 72.3 per cent of those who died were Negroes; death rates were not significantly lower than for whites. Differences by sex were greater. Though there were only 2 per cent more total male births, there were 8.4 per cent fewer premature male births and 13.6 per cent more deaths among premature male infants. Explanations for this significantly higher percentage of deaths among male infants are inadequate; examination of birth weights by sex disclosed no remarkable differences.

If fifty-three infants weighing less than one kilogram were to be excluded as "previable" (Table V), we would attain a corrected neonatal mortality of 15.9 per cent among premature infants; similarly, if eighty-eight deaths under twenty-four hours were to be excluded (Table VI), another corrected figure would be 11.8 per cent. Of all deaths among premature infants, 12.8 per cent

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TABLE III. DIFFERENCES BY RACE AND SEX AMONG PREMATURE INFANTS

	DEATHS AMONG PREMATURES		PREMATURES BORN		TOTAL LIVE BIRTHS	
	NUMBER	PER CENT	NUMBER	PER CENT	NUMBER	PER CENT
Race:						
White	41	27.7	141	23.7	1,253	24.6
Negro	107	72.3	455	76.3	3,831	75.4
Sex:						
Male	84	56.8	273	45.8	2,593	51.0
Female	64	43.2	323	54.2	2,490	49.0
Total	148	100	596	100	5,084	100
	(13.6 per cent more male premature died)		(8.4 per cent more female premature born)		(2.0 per cent more male live births)	

TABLE IV. PREMATURE MORTALITY

	DEATHS PER 100 PREMATURES	DEATHS PER 1,000 TOTAL LIVE BIRTHS
Race:		
White	29.07	32.72
Negro	23.51	27.93
Sex:		
Male	30.76	32.39
Female	19.81	25.70
Total	24.83	29.11

TABLE V. DEATHS AMONG 596 PREMATURE INFANTS BY CAUSE AND BIRTH WEIGHT

CAUSE OF DEATH	BIRTH WEIGHT					
	1,000 GM. OR UNDER	1,001-1,500 GM.	1,501-2,000 GM.	2,001-2,500 GM.	TOTAL NO.	PER CENT
Unspecified	41	20	18	9	88	59.46
Bronchopneumonia, etc.	3	6	5	2	16	10.81
Birth injuries	7	3	4	2	16	10.81
Syphilis	2	3	2	–	7	4.73
Malformations	–	2	3	2	7	4.73
Acute nutritional disturbance	–	–	2	2	4	2.70
Hemolytic disease	–	1	2	–	3	2.03
Other	–	2	2	3	7	4.73
All causes	53	37	38	20	148	100.00
Per cent	35.81	25.00	25.68	13.51	100.00	

TABLE VI. DEATHS AMONG 596 PREMATURE INFANTS BY CAUSE AND AGE AT DEATH

CAUSE OF DEATH	AGE AT DEATH							TOTAL	
	UNDER 1 HR.	1-12 HR.	13-24 HR.	25-48 HR.	3-7 DAYS	8-14 DAYS	15+ DAYS	NUMBER	PER CENT
Unspecified	12	37	8	15	8	3	5	88	59.5
Bronchopneumonia, etc.	1	1	2	1	1	1	9	16	10.8
Birth injuries	3	7	2	2	1	1	–	16	10.8
Malformations	2	2	–	2	–	–	1	7	4.7
Syphilis	–	5	–	1	–	–	1	7	4.7
Acute nutritional disturbance	–	–	–	–	–	–	4	4	2.7
Hemolytic disease	1	1	–	–	–	–	1	3	2.1
Other	–	4	–	–	–	1	2	7	4.7
All causes	19	57	12	21	10	6	23	148	
Per cent of total	12.8	38.5	8.1	14.2	6.8	4.1	15.5		
Per cent, cumulative	–	51.3	59.4	73.6	80.4	84.5	–		100.0

occurred within the first hour, 51.3 per cent within the first twelve hours, and 59.4 per cent within the first day. No such corrections are used, however, and all subsequent tabulations and remarks apply to uncorrected rates for all born alive and for any duration of stay in the delivery rooms or newborn nurseries. Leading causes for deaths are included in Tables V and VI, where they are related to birth weight and age at death, and in Fig. 1, where they are compared with those for mature infants.

Causes for eighty-eight of 148 deaths among premature infants were unspecified, that is, no conclusive clinical or pathologic opinion other than prematurity was ventured. Clinical and pathologic evidences of atelectasis and asphyxia vary only in degree among practically all premature infants who die; we felt justified in attributing only three deaths to the latter of these. Had we accepted varying degrees of atelectasis or asphyxia as adequate explanation for death, the large proportion due to unspecified causes would have been reduced. Two-thirds of the infants included in this category died within the first twenty-four hours, and about one-half of them weighed less than one kilogram. Causes for asphyxia, atelectasis, as well as death among these very small "previable" premature infants who died in the first twenty-four hours were presumably physiologic, though more careful clinical and pathologic studies might well have disclosed additional organic bases. The fact that 53 per cent of all deaths attributed to prematurity alone occurred in infants weighing more than one kilogram emphasizes the fallacy of employing birth weight as the sole index of viability or prematurity.

The presence of *bronchopneumonia* was verified by autopsy in seven of eleven instances, and good clinical bases justified such a diagnosis in the other four; the average age at death was thirty-one days. Added to this group were two deaths due to pulmonary abscesses complicating pneumonia, two attributed by pathologists to aspiration of vernix caseosa, and one to aspiration of vomitus. Low birth weights and feeding difficulties justify suspicion that repeated episodes of aspiration paved the way for most, if not all, of these respiratory causes, which accounted for about 11 per cent of all deaths among prematures.

Another sixteen of the deaths among premature infants were due to *birth injuries;* clinical diagnoses were confirmed by pathologic examination in fourteen instances. Only two of these babies survived longer than forty-eight hours.

Seven examples of *malformations,* accounting for about 5 per cent of the deaths, included esophageal and intestinal atresia, diaphragmatic hernia, hydrocephalus, anencephalus, meningomyelocele, and multiple cardiac and genitourinary anomalies. No corrective surgical procedures were justified, and only one of these infants survived longer than forty-eight hours.

Only one of seven *syphilitic* infants who died survived long enough to receive any specific therapy; in this one, inadequately treated, other infections hastened the fatal outcome. Characteristically extensive pathologic changes were described for each of these seven.

Four older premature infants died of *acute nutritional disturbances* for which no specific etiologic agent was discovered. Characterized by the all too familiar syndrome of diarrhea, dehydration, and acidosis, these disturbances

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usually appear under a variety of causes in statistical tables. We have the conviction that, with few exceptions, disturbances in fluid and electrolyte balance are far more important causes of death than the various precipitating enteric and parenteral factors. Retrospectively, we feel that most of these deaths might well have been prevented had earlier and more intensive therapy been given.

Three infants had *hemolytic disease* (erythroblastosis fetalis). Two with characteristically severe clinical manifestations died shortly after birth; the third one survived the acute stage, only to succumb later from a complicating intercurrent infection. Pathologic examinations proved each of the diagnoses.

Among seven other deaths, two were ascribed to hemorrhagic disease and two to sepsis neonatorum. One of the latter had fulminating exfoliative dermatitis (Ritter's disease) with staphylococcal bacteremia; the other had multiple pathologic evidences of bacteremia, but this was not suspected during life. Finally, there were three infants in whom undoubted clinical and pathologic evidences of asphyxia were unaccompanied by organic disease.

In addition to the leading causes discussed previously, post-mortem examinations in 102 of the 148 fatal cases among premature infants revealed fetal atelectasis in sixty-three instances, infections in fifteen, and gross hemorrhages in six, as well as a number of minor lesions considered to be unimportant in explaining death. Twenty-six had pathologic changes suggestive of asphyxia. Though the relative importance of these secondary and incidental observations could not be assessed, their very number serves to re-emphasize the problems of differential diagnosis among premature infants.

B. DEATHS AMONG MATURE INFANTS

Thirty-nine deaths among 4,488 infants born at term accounted for about one-fifth of neonatal deaths and 9 per cent of all pediatric deaths. Autopsies were completed for twenty-four of these and yielded essential agreement with clinical diagnoses in seventeen. Data concerning leading causes for deaths appear in Fig. 1, where they are contrasted with causes among premature infants, and in Table VII, where they are related to duration of life. There were too few deaths to justify comparisons of diagnoses by conventional criteria, but it was interesting to note that here, as for premature infants, mortality was slightly higher for white than for Negro and for male than for female infants. Birth weights ranged from 2.5 to 4.42 kg., averaged 2.89 kg., and only three infants weighed more than 4 kg.

TABLE VII. DEATHS AMONG 4,488 MATURE NEWBORN INFANTS BY CAUSE AND AGE AT DEATH

CAUSE OF DEATH	AGE AT DEATH							TOTAL
	1 HR.	1-12 HR.	13-24 HR.	25-48 HR.	3-7 DAYS	8-14 DAYS	15+ DAYS	
Birth injuries	2	2	5	2	1	–	–	12
Malformations	–	2	–	1	1	3	1	8
Unspecified	1	1	2	2	1	–	–	7
Bronchopneumonia	–	1	–	1	1	–	–	3
Hemolytic disease	2	1	–	–	–	–	–	3
Syphilis	1	1	–	–	–	–	1	3
Asphyxia	1	–	1	–	–	1	–	3
All causes	7	8	8	6	4	4	2	39

Autopsies performed in eight of twelve cases confirmed clinical diagnoses of *birth injuries*, and revealed gross intracranial hemorrhages in all but one. Dystocia, abnormal fetal positions, maternal toxemia or abruptio placentae apparently justified abnormal deliveries responsible for seven of these birth injuries; for the remaining five, no adequate reason for injury was found. Only one infant survived longer than forty-eight hours.

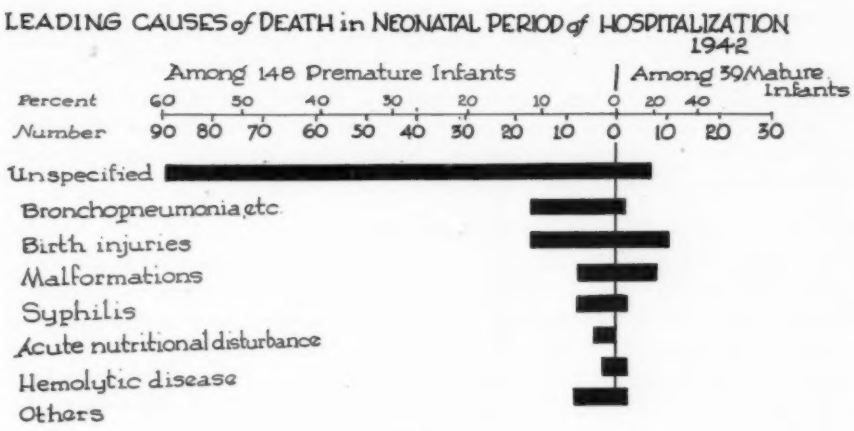

Fig. 1.

Eight deaths were explained by *multiple congenital malformations*. Most prominent among these were triloculate heart, transposition of great vessels, evisceration of entire abdominal contents, gangrenous volvulus with malrotation of midgut loop, hydrocephalus with meningomyelocele, tracheoesophageal fistula, urethral obstruction with severe bilateral hydronephrosis, and one cardiac anomaly which was not examined pathologically.

No satisfactory causes were established for seven deaths among mature infants; only one of these lived longer than forty-eight hours. Weakness, pallor, cyanosis, and disturbed respiratory patterns led to a number of conjectures regarding intracranial hemorrhage or the effects of various analgesics and anesthetics employed during labor. Five were examined pathologically, and only varying degrees of atelectasis were noted. Maternal complications required operative deliveries for four of the seven, and records indicate that there were adequate bases for suspecting fetal anoxia in these.

Pathologic diagnoses of *bronchopneumonia* were made for three infants who died in six hours, forty hours, and five days, respectively. The first of these had apparent respiratory paralysis; persistent dyspnea and recurrent strangulation in the others suggested that repeated aspiration of fluids and secretions contributed to the fatal outcome.

Three infants had clinically typical *hemolytic disease* confirmed pathologically; hydrops fetalis was the outstanding feature in two who died in less than

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one-half hour. The third infant died at five hours of suspected intracranial hemorrhage, and autopsy revealed extensive extramedullary hematopoiesis and multiple visceral hemorrhages. Three deaths occurring at one-half hour, seven hours, and seventeen days after birth were attributed to *congenital syphilis;* two of these infants also had severe hemorrhagic manifestations. Characteristic clinical features of asphyxia were encountered in three infants with no discernible organic abnormalities. Post-mortem examinations done for two were confirmatory.

In addition to these causes, included in Table VII and Fig. 1, which were in each case considered to be the most logical single explanation for death, many other abnormalities were encountered. These included fourteen examples of fetal atelectasis, five serious infections, four gross hemorrhages, and two important congenital anomalies. Pathologic evidences of asphyxia were noted in nine of twenty-four autopsies.

II. OTHER DEATHS

Among 7,386 admissions other than those included in the previous section, were ten newborn infants delivered elsewhere but admitted to this hospital after twenty-four hours, together with all other patients admitted before their twelfth birthday. As shown in Fig. 2, 27 per cent of these patients were under one year and 42 per cent under 2 years of age when admitted. The percentage of total admissions declined further in the next year, and then remained at a level varying but slightly from 5 per cent. There were 249 deaths. Comparing percentage distribution for these, a sharp fall is noted after the first year; irregularities in the percentage of deaths during each year of age after the

TABLE VIII. DEATHS AMONG INFANTS* AND CHILDREN TO AGE TWELVE BY CAUSE AND AGE AT DEATH

CAUSE OF DEATH	AGE AT DEATH: BY MONTHS UNDER AGE TWO			TOTAL UNDER AGE TWO	TOTAL OVER AGE TWO	TOTAL TO AGE TWELVE	
	0-6 MO.	7-12 MO.	13-24 MO.			NUMBER	PER CENT
Pneumonia, etc.	37	10	4	51	5	56	22.5
Meningitis	13	8	1	22	5	27	10.9
Acute nutritional disturbance	20	2	2	24	0	24	9.7
Accident	0	1	0	1	21	22	8.9
Malformations	11	5	2	18	3	21	8.4
Tuberculosis	4	1	3	8	9	17	6.8
Syphilis	13	1	0	14	0	14	5.6
Intestinal obstruction	4	2	0	6	3	9	3.6
Pertussis	2	4	1	7	2	9	3.6
Bacteremia	2	0	1	3	5	8	3.2
Rheumatic fever	0	0	0	0	7	7	2.8
Diphtheria	0	0	1	1	5	6	2.4
Diseases of the ear	4	1	0	5	0	5	2.0
Malignancy	0	0	1	1	3	4	1.6
Appendicitis	0	1	1	2	1	3	1.2
Tetanus	0	0	0	0	2	2	0.8
All other causes	5	0	2	7	4	11	4.4
Unspecified	3	0	1	4	0	4	1.6
All causes	118	36	20	174	75	249	100.0
Per cent of total				69.9	30.1	100.0	

*Excluding neonatal period of hospitalization.

fourth are explained on the basis of comparatively small numbers—altogether, deaths occurring beyond the fifth year accounted for only about 10 per cent of the total number. Almost 40 per cent of all these deaths were considered to be unpreventable, that is, the patients were dead on arrival, died in the first few minutes after hospitalization, or were discovered to have diseases for which no effective therapy could be offered. Leading causes for death, and their relative importance before and after age 2, are shown in Fig. 3 and Table VIII.

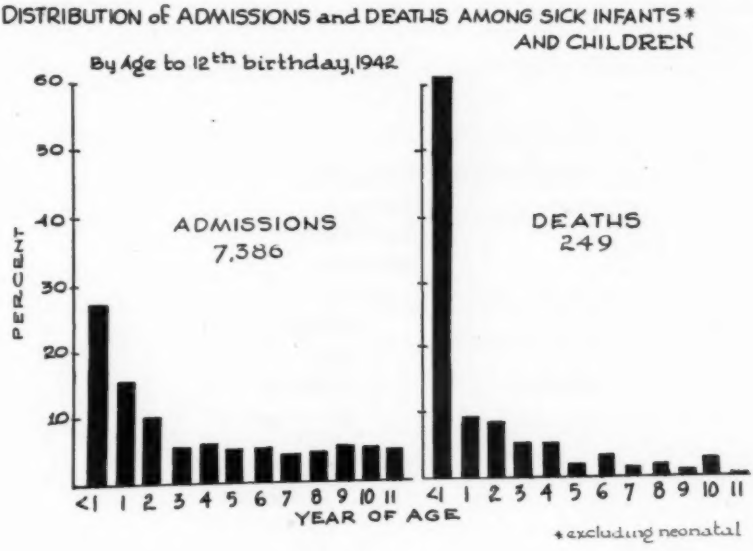

Fig. 2.

In contrast with premature and mature infants, mortality was slightly higher among the Negro than the white and among female than male children. Reasons for these statistically insignificant differences have usually been veiled in generalities concerning environmental considerations, and we discerned no better explanations.

A. DEATHS UNDER TWO YEARS

Sixty-one per cent of all deaths beyond the neonatal period of hospitalization occurred during the first year and 70 per cent before the second birthday (Fig. 2). Sixty-eight and four-tenths per cent were in Negroes and 55 per cent were in male children. Distribution by age and leading causes is shown in Table VIII; over 88 per cent of deaths in this younger group occurred before the first birthday. Tabulation by calendar months showed that the smallest number of deaths and admissions fell in July, August, and September. Considering the relatively small number of deaths attributed to each cause, we could establish no distinct seasonal pattern for specific diagnoses in this single year.

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The period of hospitalization for fifty-one patients who died of primary respiratory disease (bronchopneumonia) varied from a few minutes to as long as twenty-five days. Twenty-two of them lived less than twelve hours. The number of cases was too small to permit conclusions regarding comparative prognoses by specific etiology. Three examples of acute laryngotracheobronchitis, presumably due to mixed infection, were included. Acute and chronic nutritional disturbances, bacteremia, congenital anomalies, and extrarespiratory infections appeared frequently as important contributory factors; only one example of empyema was recognized.

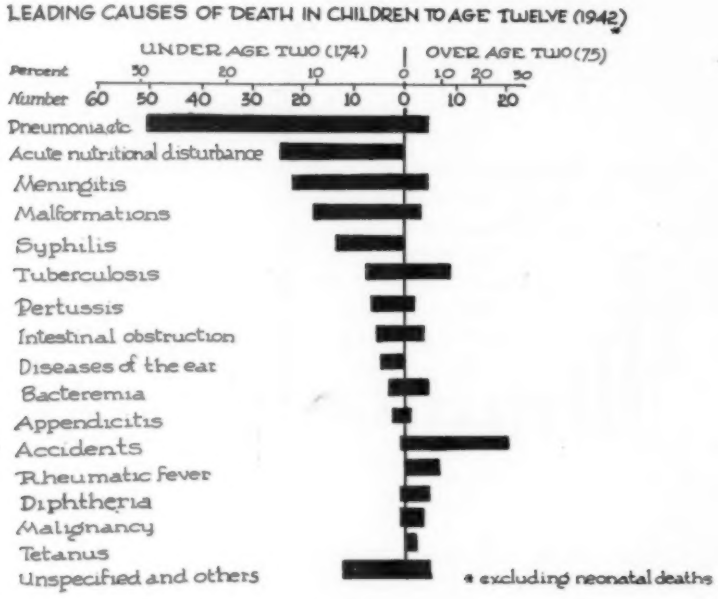

Fig. 3.

In this younger group, *acute nutritional disturbances* ranked second in importance. Among twenty-four of these, there were a variety of initiating or aggravating factors, including specific and nonspecific respiratory diseases, otitis media, or other parenteral infections, and three cases of specific enteritis due to organisms of the Shigella group. Certainly, many children whose deaths were attributed to other causes had similar but milder fluid and electrolyte disturbances. For each of these twenty-four infants, however, the acute nutritional disturbance seemed more logically responsible for death than the initiating parenteral or enteric cause.

Among twenty-two deaths due to *meningitis* other than tuberculous, *Hemophilus influenzae* was responsible ten times, pneumococcus eight times, meningococcus twice, streptococcus once, and no organism was isolated in one instance.

The duration of symptoms before hospitalization was extremely long, averaging eleven and one-half days; half of these patients had symptoms of meningitis for more than ten days when admitted, and only seven of them for less than five days. The far-advanced character of the disease was further suggested by agreement that hopeless prognoses were justified for ten of these patients at the time of admission.

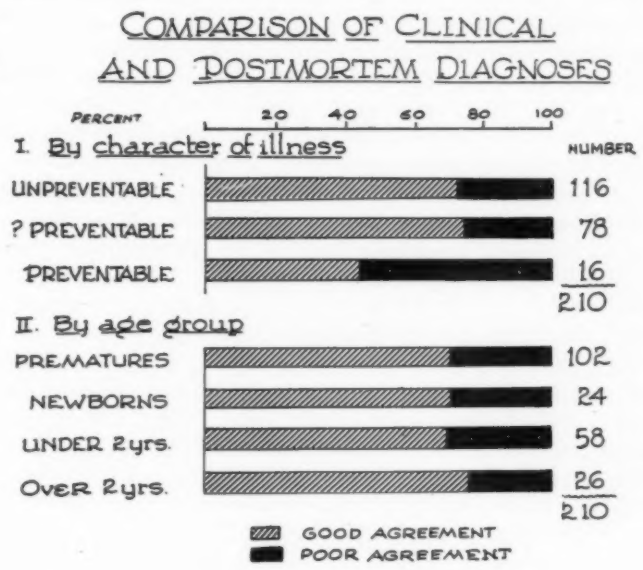

Fig. 4.

Eighteen died of *congenital anomalies;* these were characteristically multiple, but the ones judged to be most important in explaining death were found in the genitourinary system eleven times, in the central nervous system eight times, in the heart seven times, and in the gastrointestinal tract twice. The oldest patient included in this category died at thirteen months, and only seven of the infants survived for more than six months.

There were fourteen deaths attributed to *congenital syphilis* among thirty-six infants hospitalized for this disease. Usual therapy consisted of varying combinations of arsenicals and bismuth, which appeared to hasten death in at least five. The average age at death was 15 weeks, with a scatter from 7 to 36 weeks; none had been treated for syphilis prior to hospitalization.

All of eight deaths from *tuberculosis* were classed as unpreventable; no effective medical therapy could be offered for widespread involvement present at admission. In six of these, meningeal lesions predominated; all had miliary and extensive pulmonary disease. We have previously emphasized the importance of tuberculosis as a cause for death in infants and children at our hospital

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and pointed out that during the last decade it accounted for 9.8 per cent of all deaths at this hospital and 6.1 per cent of deaths in children.[1]

Pertussis, in each case accompanied by bronchopneumonia, was responsible for seven deaths among seventy-nine patients hospitalized for this disease. All seven deaths occurred between the ages of 3 and 13 months, five of them early in the third week of the disease and the other two in the seventh and ninth weeks. There is no doubt that many others were recognized and treated in out-patient departments.

There were six fatalities among fourteen infants admitted for *intestinal obstruction*. Three were due to intussusception; in each instance typical symptoms had been present for more than six days before hospitalization. One was ascribed to incarcerated inguinal hernia, one to volvulus and gangrene after postoperative adhesions, and one to extrinsic duodenal obstruction.

Direct extension of infection, infections elsewhere in the respiratory tract, or acute nutritional disturbances made it difficult to attribute death primarily to *otitic disease*, but we found no alternative for five examples so included in Table VIII and Fig. 3. Two deaths from *appendicitis* followed prolonged illness, spontaneous rupture, and generalized peritonitis; both patients were moribund at admission, and neither responded to diligent therapy.

Three examples of *bacteremia* included one due to *Staphylococcus aureus*, with numerous visceral abscesses, one due to an unidentified gram-positive bacillus, and one presumptive, manifested by extensive furunculosis in a debilitated infant. There was only one death from *diphtheria* under age two, one attributed to *aspiration of feeding*, one to *cerebellar astrocytoma* in an infant of 16 months. Included among deaths due to all *other causes* were three examples of intracranial hemorrhage, two following birth trauma in infants delivered outside the hospital and one occurring spontaneously in the course of an upper respiratory infection. There was one case of acute bacterial endocarditis in an infant of six weeks, one of severe hemolytic disease (erythroblastosis), one of primary peritonitis and one of acute leucemia. There were four unexplained deaths, each occurring so soon after admission that no satisfactory diagnostic studies were made.

B. DEATHS AFTER AGE TWO

Thirty per cent of 249 deaths beyond the neonatal period of hospitalization occurred in children who had passed the second birthday, and 59 per cent of these were less than 5 years of age when admitted. Fifty-six per cent were Negro, and 57 per cent were male. Distribution of admissions and deaths by age are shown in Fig. 2, and leading causes for death in Fig. 3 and Table VIII. Because of the small number who died of any single cause in this age group, comparisons by sex, color, and age were not made. Forty per cent of these deaths after the age of 2 were considered to be inevitable at the time the patients were admitted.

Accidents, accounting for twenty-one deaths, led the list of causes beyond age two. There were seven patients with extensive burns, three with crushing injuries, three examples of acute lead poisoning; two were attributed to an

anesthetic or its immediate sequelae, two to aspiration or ingestion of foreign body, two to trauma leading to intracranial hemorrhage, one to gunshot wound, and one to drowning.

Tuberculosis was responsible for nine deaths. Only pulmonary lesions were demonstrable in four patients, and the other five had extensive visceral involvement with meningitis predominating. The shortest duration of symptoms recorded before hospitalization was two weeks, the longest two years, and the mean duration was about six months. Tuberculosis was suspected or proved at the time of admission for six, when four of these deaths were considered unpreventable. The average duration of hospitalization was seven days, with a range from ten minutes to fifteen days, emphasizing again the often fulminating course of reinfection forms of this disease in children.

Three of seven deaths due to *rheumatic fever* with heart disease occurred during the fourth year of life; the oldest patient was 11 years old. Diagnoses, apparently satisfactorily established by clinical criteria, were proved pathologically for four who were examined at autopsy. The average duration of hospitalization was thirty-five days; the total duration of illness varied from two weeks to six and one-half years. All patients were lifelong residents of this State. During this same year, diagnoses of rheumatic fever and heart disease were made for seventy children in this age group.

Among five deaths due to *bronchopneumonia*, one followed severe laryngotracheobronchitis, one was accompanied by lung abscess, and one by bronchopleural and esophagopleural fistulae complicating empyema. Five children died of *diphtheria*, all under 6 years of age; four had predominantly laryngeal involvment, and two died within an hour of arrival at the hospital. All were promptly recognized and all received diligent specific and supportive therapy.

Among five deaths from *acute purulent meningitis*, one was due to *Staph. aureus*, one to pneumococcus type VI, and no organisms were recovered from the other three. The second of these appeared to be due to extension of otitic disease, but no adjacent foci were found for the others. Closely related to the last group were five examples of *staphylococcal bacteremia*; three of these patients had terminal meningitis. One was associated with exacerbation of chronic osteomyelitis, one with cavernous sinus thrombosis, and one with a sickle-cell crisis.

Of three deaths from *intestinal obstruction*, two were due to insussusception, the other to adhesive bands following an earlier surgical procedure. Among three *congenital anomalies* responsible for death, two were cerebral and one cardiac; all patients were chronically invalidized and had terminal respiratory infections. *Malignancies* ranked next, with one retinal glioma, one craniopharyngioma, and one unidentified but inoperable cerebellar tumor. Both children who died of *pertussis* had extensive bronchopneumonia, and one of them had accompanying acute hemorrhagic nephritis with cardiac failure. Both cases of *tetanus* followed deep puncture wounds, were far advanced at the time of admission, and failed to respond to appropriate therapy. Death of one child was attributed to *appendicitis* complicated by peritonitis, subdiaphragmatic abscess, fecal fistula, and extreme cachexia.

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Among four deaths from other causes, one was ascribed to measles with bronchopneumonia, one to acute nephritis with cardiac failure, one to chronic adhesive pericarditis (Pick's syndrome), and one to aspirational pneumonitis following corrosive esophagitis.

COMPARISONS OF CLINICAL AND POST-MORTEM DIAGNOSES

Clinical diagnoses were compared with those recorded after autopsy, and grades were assigned for degrees of agreement. Crude correlations could then be made according to a number of variables. We found that pathologists confirmed clinical diagnoses for cause of death, with occasional minor and incidental additions, in from 70 to 75 per cent of the cases they examined. No significant change in quality of clinical diagnoses could be related to age of patients or duration of symptoms before admission, though correlations improved with duration of hospitalization; good agreement was observed in 66 per cent of patients who had been hospitalized for less than one week but increased to 82 per cent in those hospitalized for more than one week. Little point would be served by including here all the data and charts from which such comparisons were made; only a sample is included as Fig. 4. As one would expect, poorest agreement of clinical and post-mortem diagnoses was obtained for deaths we had classified as preventable. Unfortunately, autopsies were secured for only 51 per cent of all pediatric deaths that year. Though our grading of correlations may have been severe, and the number of cases small, it was both stimulating and disappointing to find that autopsies revealed clinically unrecognized major lesions or unsuspected causes for death in the large percentage indicated as "poor agreement" in Fig. 4.

SUMMARY

During 1942 there were 436 deaths among 12,470 children admitted under age 12. Forty-three per cent of all pediatric deaths occurred during the neonatal period of hospitalization for 5,084 infants born alive in the hospital; this group constitutes the basis for the first portion of our study, in which premature and mature infants are considered separately. The second portion is concerned with the remaining 57 per cent of all pediatric deaths among 7,386 infants and children from one day to 12 years of age at the time they were admitted; here patients younger and older than 2 years of age are considered separately.

Leading and incidental causes for death, and pertinent differences by age, race, and sex were analyzed and discussed for each group. Finally, crude correlations of clinical and post-mortem diagnoses were made for 210 patients examined pathologically.

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NONTUBERCULOUS PULMONARY CALCIFICATION

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THE conception that calcium deposits in the lungs or at their hili are pathognomonic of tuberculosis has long been well established in the minds of medical men, both clinicians and roentgenologists. In recent years much evidence has been accumulated to show that there are other common causes of pulmonary calcification.

Gass[1] conducted a careful study of 1,281 children in Tennessee and found many with negative tuberculin tests and calcified hilar glands. He made no effort to explain this discrepancy. Long and Stearns,[2] after reviewing over 40,000 chest films of American soldiers with calcium deposits in the chest, reported that the incidence of such deposits varies in different localities and is greatest in the East Central United States. They concluded that the great majority of the cases of pulmonary calcification were due to tuberculosis but that some were due to fungus diseases.

Lumsden and Dearing[3] conducted a careful and extensive study in several counties of five South Central States. In Giles County (Tenn.) alone, they found 14,000 persons with calcium deposits in the chest and only 10,000 with positive tuberculin tests. Even more striking is the fact that they found a much higher incidence of pulmonary calcification in some of these counties than in others where conditions relative to tuberculosis seemed to be the same. A county with a high incidence of pulmonary calcification often lay next to one with a low incidence. Those counties with a high incidence of pulmonary calcification are underlaid with limestone (with a high percentage of calcium in the drinking water), whereas those of low incidence are underlaid with a flint type of rock. These soil conditions were determined by the U. S. Geodetic Survey. These facts suggest that one must consider factors other than disease.

Olson[4] observed a high incidence of pulmonary calcification in Ross County (Ohio), which could not be accounted for by tuberculosis. He concluded that these cases were due to a common unrecognized disease, perhaps ascariasis. But he could produce no definite evidence of this. This study was based on the observation of 500 individuals. An unusually careful study was conducted by Aronson[5] of the Phipps Institute among North American Indians. He found, as part of his study, that in the Pima Agency of Arizona alone there were 704 children with negative tuberculin tests. Of these, 102, or 14.5 per cent, had calcified hilar nodes. These were not false negatives due to anergy, because one year later he produced a positive tuberculin test in fifty-six out of sixty-two such children by the injection of BCG vaccine, that is, attenuated live tubercle bacilli. He concluded that these nontuberculous calcium deposits may be due to *Coccidioides immitis* infections. Geever[6] suspected that tuberculosis is not the only cause of pulmonary calcification.

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Palmer[7] reported a study of 3,105 student nurses, conducted cooperatively by the National Tuberculosis Association and the United States Public Health Service. Of this total number, 294 had pulmonary calcification. Approximately 80 per cent of these were tuberculin negative and were regarded as not having tuberculous infection of any sort. A high percentage of these had a positive skin reaction to histoplasmin. The author concluded that the calcification was probably due to a mild subclinical infection with *Histoplasma capsulatum*.

Our own series, though small, has been studied intensively and in a somewhat different manner. Our curiosity was aroused by children with negative tuberculin tests and calcium deposits in the chest. By chance, fourteen such children were encountered in the outpatient department. All 14 were tuberculin tested with PPD (purified protein derivative of Seibert[8]). They were completely negative to both first test strength and second test strength PPD. They were rechecked a year later not only by these two tests but also by the Vollmer patch test. The PPD tests are generally regarded as the most accurate of all tuberculin skin tests. The fourteen children were consistently negative to all these tests.

Bronchoscopy.—In order to further rule out the possibility of false negatives, all fourteen were bronchoscoped. The appearance of the mucous membrane was studied and recorded. The bronchial secretion was aspirated and studied by direct smear, culture, and guinea pig injection. The mucous membrane at the bifurcation and in the main bronchi in nine out of the fourteen was described as somewhat abnormal. Some portions of the inspected areas were slightly reddened, thickened, or edematous. These changes were neither striking nor characteristic of any known disease.

Bacteriology.—Acid-fast bacilli were found by direct smear in the aspirated secretion from only one patient, although careful search was made for them in each. This patient was a child with the typical clinical characteristics and laboratory findings of Boeck's sarcoid. This rare disease is regarded by some investigators as a tuberculous-like disease, by others as a mild, atypical, hard tuberculosis with anergy to the tuberculoprotein. This disease, therefore, has a negative tuberculin reaction. Admittedly, it is difficult to demonstrate acid-fast bacilli in Boeck's sarcoid. We feel that the findings in this case are some evidence of the efficacy of the bronchoscopic method of study.

In every case except one, the aspirated secretion was injected into a guinea pig. Ten of these thirteen pigs lived the usual eight weeks, were killed and autopsied, but none had tuberculosis. The other three died prematurely of other infections. Fusiform bacilli and spirochetes were demonstrated by direct smear of the aspirated secretion in eight cases.

X-ray Study.—Calcium deposits were demonstrated at one or both hili in every patient. One patient showed calcification in the right third interspace not unlike a Ghon tubercle. The calcium deposits were not heavy in any patient.

Other Laboratory Data.—The red, white, and differential blood counts and hemoglobin estimations were in the normal range. Urinalysis and complement fixation tests for syphilis were negative for every child.

Clinical Data.—These children were both Negro and white, male and female, with ages ranging from 3 to 14 years (average 8). Only one had had known exposure to tuberculosis. Eight of these children had a history of frequent colds with a cough that was usually described as persistent or chronic. These children were all well nourished and appeared normal to cursory inspection.

Histoplasmin Skin Tests.—Histoplasmosis is usually considered a rare and serious infection. However, the fact that a large number of persons without history of serious disease are skin sensitive to histoplasmin raises this question: May there not be an unrecognized subclinical form of histoplasmosis detectable only by skin test?

Twelve of these fourteen children were skin tested with histoplasmin. Each was injected intradermally with 1/10 c.c. of diluted histoplasmin prepared in the laboratory of St. Luke's Hospital from an individual with a fatal infection with *Histoplasma capsulatum*, reported by Van Pernis and co-workers.[9] The technique of preparation is outlined in their report. The site of injection on the forearm was observed for one hour for immediate reaction and after twenty-four hours for delayed reaction. The formation of a 10 mm. wheal or skin induration with redness was considered a positive reaction. Such a wheal appeared in six of the twelve children. In each of the six positive cases the indurated area varied from 1½ cm. to 2½ cm. with a red area usually extending well beyond the induration and ranging up to 4½ cm. in diameter.

This reaction in all six patients occurred within one hour, usually within fifteen minutes. In two of the six patients, induration and redness were still present after twenty-four hours. In the other four, they had disappeared by the second day. None of the six had a delayed reaction, that is, one appearing on the second day.

SUMMARY

We have presented fourteen children with clearly negative tuberculin tests. One child had Boeck's sarcoid involving the lungs without cough. Acid-fast bacilli were demonstrated by direct smear in the secretion aspirated through the bronchoscope in this one patient only.

On the basis of this as well as other experiences, we regard bronchoscopic methods of study in questionable cases of tuberculosis as very valuable.

All remaining thirteen children with negative tuberculin tests had small but definite calcium deposits in the chest. A thorough clinical study, including bronchoscopy and bacteriologic study of the aspirated secretions, failed to produce any evidence that these children had or had had a tuberculous infection.

Eight of these thirteen patients with pulmonary calcification had some change in the mucous membrane at the bifurcation or in the main bronchi. Eight of the thirteen had a history of frequent colds or persistent coughs. Twelve of the thirteen were skin tested for histoplasmin. Six of these twelve gave an immediate reaction to histoplasmin. There were no delayed reactions.

CONCLUSIONS

On the basis of reports in the literature and our own experience, we feel justified in concluding definitely that there are important causes of pulmonary

calcification exclusive of tuberculosis. It is generally recognized that tuberculosis is not the sole major cause of calcification in other parts of the body. Why should the chest be an exception? We believe tuberculosis is the most frequent cause of calcium deposits in the chest. However, the other causes are not rare or inconsequential. They should *not* be ignored as they have been in the past.

Just what these other causes are, is a question still not completely answered. There is suggestive evidence that a mild subclinical histoplasmosis may be one of them. Ordinary recurrent respiratory infections may be another.

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RECEDING CHIN AND GLOSSOPTOSIS

A Cause of Respiratory Difficulty in the Infant

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ONE of the causes of cyanotic attacks in newborn infants which is commonly overlooked is hypoplasia of the mandible, or receding chin, occasionally referred to by the name of Pierre Robin syndrome. This condition, described in 1929 by Pierre Robin,[1] is often found in association with cleft palate, foreshortening of the genioglossi muscles, and inspiratory retraction of the sternum.

In hypoplasia of the mandible, ptosis of the tongue causes mechanical obstruction of the larynx with cyanosis, difficulty in swallowing, marked respiratory embarrassment with severe retractions of the sternum, and subsequent malnutrition. The symptoms are aggravated during feeding.

The clinical picture resembles that of true obstructive laryngeal dyspnea and is caused by mechanical obstruction. The infants may die of starvation, called glossoptotic cachexia by Robin,[2] or of asphyxia, before the condition is recognized.

CASE REPORT

A 7-week-old male infant was admitted to the Children's Hospital, with a history of difficulty in swallowing and breathing since birth and cyanotic spells for one day.

The infant was born after 8 months' gestation to a 23-year-old primipara. Delivery was normal, and the birth weight was 5 pounds, 12 ounces. At 6 weeks of age the weight was 6 pounds, 6 ounces. It remained stationary during the next week. Because of the difficulty in swallowing, the intake was limited to 1 to 2 ounces of S.M.A. at a feeding. Orange juice and oleum percomorphum had been offered. The mother stated that the baby occasionally arched his back to facilitate the breathing. For two weeks before admission the infant had vomited at least once a day, and the vomiting increased in frequency during the two days before entry.

During this period an upper respiratory infection had increased the nasal obstruction, and in the twenty-four hours before admission several cyanotic spells had occurred.

Examination revealed an acutely ill, malnourished, poorly hydrated infant with noisy respirations, dyspnea, cyanosis, and severe retraction of the sternum on inspiration. There was also considerable nasal obstruction and coryza.

The head measured 14 inches, the chest 12.6 inches, the abdomen 11.3 inches, and the length 21 inches. The cry was hoarse and guttural. The face showed a marked receding chin (see Fig. 1). A left strabismus was present. The ears protruded outward. There was a cleft of the posterior portion of the soft palate and uvula, and the tongue was displaced posteriorly and rested

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against the pharyngeal wall occluding the respiratory passages. The chest was funnel shaped, and breath sounds came through poorly on pulmonary auscultation. The abdominal examination was negative. Neurological examination, except for unsustained ankle clonus, was not remarkable.

Laboratory Findings.—Urine examination was within normal limits. The hemoglobin was 71 per cent; the white blood count was 11,150 with 60 per cent polymorphonuclear leucocytes, 33 per cent lymphocytes, 6 per cent monocytes and 1 per cent eosinophiles. Blood serum calcium was 10.5 mg. per 100 c.c., and serum inorganic phosphorus was 3.5 mg. per 100 c.c. The Mantoux reaction to 0.01 mg. of old tuberculin was negative. The blood Kahn test was negative.

Fig. 1.—Infant at 8 weeks of age, showing receding chin and sternal retraction.

An x-ray of the chest revealed bilateral emphysema, and the heart was not abnormal.

Course.—The child had a normal temperature throughout his hospital stay, but continued to have cyanotic spells and severe respiratory distress and ate very poorly. He was extremely restless and irritable and required small doses of phenobarbital for sedation.

He was placed in an oxygen tent, fed with a Breck feeder, and given frequent supplemental clyses of 5 per cent dextrose and saline. He was also

given penicillin, 5,000 units every three hours intramuscularly, as a prophylactic against bronchopneumonia. The nose was cleared frequently by suction, and 0.25 per cent neosynephrin nose drops were instilled from time to time. The child frequently assumed the opisthotonic position for relief. It was also noted by the nurses that respirations seemed easier when the infant lay on his stomach.

Fig. 2.—Infant wearing headgear.

The tentative diagnosis on admission was congenital laryngeal defect or web, superior aperture collapse, and upper respiratory infection, and the question of a tracheotomy was seriously considered by the otolaryngologist. Four days after admission, the infant was laryngoscoped and no congenital web or obstruction was found. There was collapse of the structures of the superior aperture. With the laryngoscope in place, it was noted that with the base of the tongue raised, the child could breathe without obstruction or sternal retraction. At this time the correct diagnosis became apparent.

The infant was placed on his abdomen with a small pillow under the upper part of the chest. The cyanosis improved and the respiratory difficulty diminished. The infant was fed in this position from a bottle with the child reaching outward and upward.

A headgear was then devised for the infant with a padded metal bar around the head and padded metal bars at the sides which extended downward and slightly forward; felt pads which impinged between the posterior rami of

the mandible and the external auditory meatus created pressure and pushed the jaw forward as shown in Fig. 2. The headgear was placed on the child eleven days after admission. Wearing the apparatus, the infant's respiration improved and he could be held and fed upright, with substantial increase in the intake of the formula. Thirteen days after admission he was discharged, weighing 7 pounds, 7 ounces, on an evaporated milk formula. Subsequently, the headgear had to be modified with cross tapes across the top of the head to prevent it from riding downward over the ears.

Fig. 3.—Child at one year, showing residual sternal retraction.

The infant wore the apparatus for a month after discharge. He is now one year old, and when seen at monthly intervals was free of cyanosis or respiratory difficulty, despite frequent upper respiratory infections. Feeding has presented some difficulty, with the infant eating poorly and vomiting at times. Weight gain has been slow, but growth and development have been normal. The funnel chest is improving and is less marked (see Fig. 3). At one year the child's height is 29 inches, the weight is 18 pounds, 6 ounces. The head measures 18 inches, the chest 18 inches, and the abdomen 16½ inches. The mandible has grown to some extent but still recedes somewhat.

REVIEW OF LITERATURE

Several case reports have appeared in the literature.[3-11]

Theories advanced to explain the etiology of the development of hypoplasia of the mandible include that of Kiebel and Mall,[12] who attribute it to a

simple arrest of the developmental process. Schwartz[4] feels that the presence of other associated abnormalities in infancy confirms the theory of Kiebel and Mall. Pierre Robin[1] in his monograph enumerates still other associated clinical manifestations which he feels result from the pre-existing glossoptosis and are secondary to the respiratory and swallowing difficulties. These systemic manifestations are protruding ears, kyphosis, scoliosis, genuvalgum, strabismus, adenoids, dental caries, pigeon breasts, flat feet, abdominal ptosis, and cryptorchidism.

In our patient, strabismus, protruding ears, and pigeon breast were present in infancy.

Warkany[13] suggested that malnutrition of the embryo might be a possible cause, and was able to produce hypoplasia of the mandible, radius, ulna, tibia, and fibula, plus cleft palate and syndactylism in rats on diets deficient in riboflavin.

Davis and Dunn[5] believe that hypoplasia of the mandible is due to the weight of the fetal body in utero causing marked flexion of the neck with resulting pressure on the mandible from forceful contact with the fetus's sternum. If this occurs early enough before the mandible is calcified, the deformity is enhanced. Pressure has also been thought to be a factor in the production of the cleft palate.

The genioglossi muscles are responsible for drawing the tongue forward, since their insertion is on the symphysis menti of the lower jaw. With hypoplasia of the jaw and backward displacement of the mandible, the traction of the genioglossi cannot prevent the tongue from dropping backward, and obstruction of the superior aperture occurs.

TREATMENT

It is evident that the cause of the attacks of cyanosis and of the respiratory and feeding difficulties is on a mechanical basis due to glossoptosis. When the head is extended, respiration is facilitated and the jaw is brought forward. Immediate therapy should consist of oxygen; the child's face should be placed down in the prone position with the chest elevated by a small pillow, and the infant should be encouraged to nurse reaching outward and upward, like the young of the lower animals. Robin[1] calls this orthostatic nursing. After and during feeding, Robin[2] also advises holding the infant erect, without shaking, for ten minutes until the air is expelled orally.

Subsequent treatment for our patient consisted of the construction of a headgear, as first recommended by Eley and Farber[5] and later modified by Llewellyn and Biggs.[14]

Llewellyn and Biggs[14] feel that the mandible eventually grows to normal proportions equalling the growth of the maxilla, in all cases except where there is ankylosis present with atrophy of the genioglossi muscles. The treatment should, therefore, be directed toward artificial means of keeping the jaw forward until adequate muscle action and development has been established. The length of time for wearing the brace depends probably on the time it takes for the infant to overcome the glossoptosis. In our patient, it was one month.

Callister,[15] however, reported a case in which he had no success with the head brace. He employed skeletal tractions of the mandible with good results. Davis and Dunn[8] used a curved metal form made to fit the upper lip and connected to the nursing bottle through an easily adjustable attachment which permitted lengthening the distance between the nipple and the infant's mouth. This made the infant thrust out its lower jaw in order to grasp the nipple. Babcock[16] described the method by which the temporomandibular structure in front of the external auditory canal is disarticulated, the mandibular heads forced anteriorly, and the gaps filled with costal cartilage.

Hensel[17] performed an osteotomy on the ascending rami of the mandible and then grafted bone into the symphysis menti. These are rather extensive surgical procedures to perform on newborn infants and are reserved for those older children whose mandibles do not develop normally.

TABLE I. REVIEW OF THE LITERATURE ON HYPOPLASIA OF THE MANDIBLE

AUTHOR	AGE	RECEDING CHIN	GLOSSOPTOSIS	CLEFT PALATE	RETRACTION OF XIPHOID	CYANOSIS
Eley and Farber	6 weeks	Yes	Yes	Yes	Shown in photograph but not described	Yes
Eley and Farber	3 days	Yes	Yes	Yes	Inspiratory embarrassment	Yes
Eley and Farber	10 days	Yes	Yes	Yes	Not described	Yes
Eley and Farber	3 days	Yes	Yes	Yes	Inspiratory embarrassment	Died
Schwartz	Newborn	Yes	Yes	Yes	Yes	Respiratory difficulty; died
Lannelongue and Menard	?	Yes	Yes	Yes	Not described	Not described
Lannelongue and Menard	?	Yes	Yes	Yes	Not described	Not described
Lannelongue and Menard	?	Yes	Yes	No	Not described	Not described
Weisengreen and Sorsky	Newborn	Yes	Yes	Not mentioned	Not mentioned	Died
Davis and Dunn	3 weeks	Yes	Yes	Yes	Not mentioned	Yes
LaPage	2 weeks	Yes	Yes	No	Not mentioned	Yes, died
Llewellyn and Biggs	3 weeks	Yes	Yes	Yes	Not mentioned	Yes
Children's Memorial Hospital, Chicago	2 weeks	Yes	Yes	Yes	Suprasternal retraction; inspiratory	Yes
Nisenson	7 weeks	Yes	Yes	Yes	Yes	Yes
Lenstrup	6 weeks	Yes	Yes	Yes	Inspiratory embarrassment	Yes
Lenstrup	1 week	Yes	Yes	Yes	Contractions of thorax; inspiratory	Yes
Lenstrup	1 week	Yes	Yes	Yes	Yes	No
Shukowsky	Newborn	Yes	Yes	Yes	Inspiratory difficulty	Asphyxia, died
Shukowsky	Newborn	Yes	Yes	No	Inspiratory difficulty	Yes
Totals, 19 Cases		19	19	15	7—Inspiratory embarrassment 4—Xiphoid retraction	11

DISCUSSION

Pierre Robin[1] first described the mechanical effects of ptosis of the tongue in his monograph. From subsequent papers which appeared in the literature, it is evident that a definite combination of physical findings are present (see Table I).

Nineteen cases have been reviewed and charted. All of these patients showed deficient development of the lower jaw and glossoptosis. Fifteen had an associated cleft palate. In four there was sternal retraction. In seven others there was inspiratory embarrassment. In the others, nothing is mentioned about the presence or absence of sternal retraction. Eleven had cyanotic attacks.

It is apparent that the presence of receding chin, glossoptosis, cleft palate, and sternal retraction constitutes a clinical syndrome.

SUMMARY

1. A case of hypoplasia of the mandible and glossoptosis, associated with cleft palate and inspiratory retraction of the xiphoid process, is presented.

2. Associated clinical findings are cyanosis, respiratory embarrassment, difficulty in swallowing, and malnutrition.

3. Treatment is primarily postural with the infant placed prone, a pillow under the upper thorax, and the child fed on its stomach with the head extended.

4. The use of a headgear is advocated, devised to keep the mandible forward.

The writer wishes to express his appreciation of the valuable assistance received from Dr. Elvira Goettsch.

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Case Reports

CANDIDA ALBICANS INFECTION IN A CHILD

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THE reports of fungus infection in the literature before 1930 have little meaning as a result of faulty identification of the organisms. In the last decade the peculiarities of fungi have become better known, and mycotic infections have been increasingly reported. Infections of all systems have been described, but rarely for the urinary tract. These have been reported by Oomen,[1] Wessler, C. S.,[3] and Moulder[2] with good biological proof.

CASE REPORT

History.—A female infant, 7 months of age, was admitted Oct. 14, 1946, with the complaint of passing blood per anum. This was associated with colicky pain and a foamy diarrhea. Hematuria had not occurred. Aside from oral thrush a few weeks previously the infant had not been ill. The family history was irrelevant.

Clinical Examination.—On admission the weight was 6 kg. The infant was restless and vomited. The mucous membrane of the mouth and throat appeared normal. The skin was pale, and scattered over the body were erythematosquamous plaques varying in size from a dot to a centimeter in diameter. The heart and lungs were negative. The abdomen was not distended but was painful to palpation. Peristalsis was visible. Blood was discharging from the rectum, and the anal sphincter was lax. Dark clots followed digital examination. The vulva was covered by a white membrane, and the mucous membrane was inflamed. There was no vaginal discharge.

Entry Laboratory Findings.—The blood count showed 3,500,000 red blood cells, 70 per cent hemoglobin, 15,000 white blood cells, and 320,000 thrombocytes. A differential count showed 1 eosinophile, 6 stab cells, 44 segmented cells, 41 lymphocytes, and 1 mononuclear cell. Bleeding, coagulation, and prothrombin times were within normal limits.

Hospital Course and Subsequent Laboratory Data.—As the signs suggested intestinal obstruction, a surgical consultation was held, and an exploratory laparotomy was done on the day following admission. No abnormality of the intestine was found. After a rather stormy postoperative course with continuous intravenous infusion for four days of casein-hydrolisate and glucose and nothing by mouth, the hemorrhage and diarrhea stopped. The temperature was remittent up to 39° C. and was not affected by 100,000 units of penicillin daily. During this time the urine showed no abnormalities except a few leucocytes.

As there was seemingly pain and tenderness on pressure over the mastoids, an opening of the mastoid was made but no hidden infection was found. The temperature finally became normal although penicillin had been stopped several days previously.

On October 27, yeast cells grew out on a glucose agar culture of a catheterized specimen of urine, and the urinary sediment showed macroscopic white masses, which proved to be collections of mycelial threads showing blastospores and enmeshed leucocytes (Fig. 1). Subsequent cultures proved to be solely

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C. albicans (Robin-Berkhout, 1923). The identification was made by the Yeast Division of the Centraal Bureau Voor Schimmelcultures at Delft, Holland, Prof. Dr. Kluyver the director.

Urinary tract examination:

Urine: The pH reaction was 5.8; the specific gravity was 102.5; there was a trace of albumin and no sugar. Sediment showed masses of mycelia. Leucocytes were present in clumps, and there were a few red cells. There were no casts. Cultures for bacteria were negative.

Renal function: Renal function appeared to be good (Rowntree 63.5 per cent). Urea and chloride in the blood serum were normal.

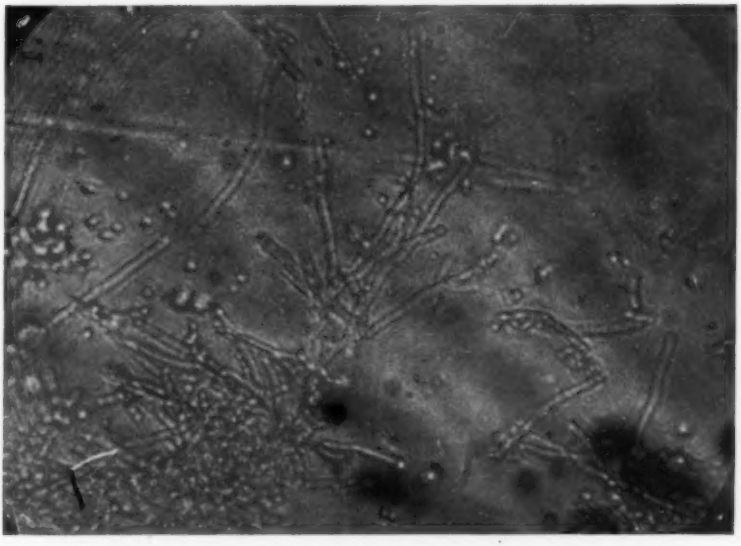

Fig. 1.—Mycelial threads showing blastospores and enmeshed leucocytes.

Cystoscopy: The bladder capacity was normal, as was the mucous membrane, except near the orifice of the left ureter, where small, ivory-white lines were seen. The orifices were not patent. Catheterization of the left ureter was easy, and 5 c.c. of cloudy urine was obtained, showing a trace of albumin, 4 leucocytes per high-power field, and a few red cells. There were no bacteria. The centrifuged sediment showed fungi which grew out on culture as *C. albicans.* A retrograde pyelogram showed a dilatation of the left ureter (Fig. 2) with no abnormality on the right side.

Proctoscopy: Proctoscopy showed a red and swollen mucous membrane for the first 6 cm. In the rectal ampulla were marble-sized white masses considerably obstructing the lumen of the bowel. Removal of these masses caused brisk hemorrhage. There were found to be masses of packed mycelial threads of *C. albicans.*

Skin: Cultures from the skin lesions were negative.

Lungs: Monthly roentgenograms showed a gradually increasing density in the right middle and lower lobes and left upper lobe. The hilar shadow was broadened. No calcified foci were present. Mucoid material from the

tracheal bifurcation was obtained, which, on smear, revealed branching yeast cells. Although great care was taken, it is not absolutely certain that there was no oral contamination. Cultures from the material were negative.

Other examinations: Fasting stomach contents were free from tubercle bacilli, and guinea pig inoculations were negative. The Mantoux reaction was repeatedly negative.

Fig. 2.—Retrograde pyelogram showing dilatation of the left ureter.

Blood vitamin A content was 8.3 I.E. and 17 gamma carotene per 10 c.c.

Roentgenograms of wrists and fingers showed no abnormalities.

The Wassermann and Meinicke reactions were negative. Complement fixation tests for typhoid, paratyphoid, *Bacillus abortus,* and *Spirochaeta icterohaemorrhagiae* were negative. The blood cultures were repeatedly negative.

Course of Disease and Treatment.—A month after admission the child improved spontaneously. Yeast cells in urine and feces decreased in number. This improvement started before the child received large doses of potassium iodide with Cibazol. (Later it was brought to our notice that yeast produces large quantities of para-aminobenzoic acid so that Cibazol was useless.)

A fortnight after cessation of this treatment the urine was free of yeast and the skin clear for the first time. Another fortnight and the feces were also free of yeast.

A diet containing carbohydrate in the form of lactose exclusively had been given in an effort to free the alimentary tract of *C. albicans,* as these organisms do not ferment lactose (Buchanan[4]). The urine was made alkaline with sodium bicarbonate.

Because yeast infection of the lung was feared,[5, 6] serum of rabbits immunized with *C. albicans* was administered, but the serum caused such severe reactions that it was abandoned.[7]

Special Skin Tests Performed.—Table I shows the skin tests performed. Scarification reactions were positive only with yeast cell suspensions, and as the child improved these reactions became negative. Intracutaneous injection with living cells and with extracts were positive and gave on repetition a shortened reaction time. No atopic (Hopkins[7]) or anaphylactic reactions were seen. There were neither general reactions nor reaction at previous injection sites. No cross reactions with other fungi or yeasts could be elicited, not even with species of the *Candida genus.* The skin reactions in the control children were negative.

The yeast isolated from the patient was investigated as follows:

1. A series of cultures was treated with x-ray doses of 100, 250, 500, 1,000, 2,000, and 4,000 R. without affecting the growth rate (Jacobson[9]).
2. Anaerobic and aerobic cultures grew equally well.
3. A rabbit weighing 1.75 kg. was injected intravenously with 0.5 c.c. of living yeast cell suspension of 2×10^6 organisms per cubic centimeter. The animal died two days afterwards. Autopsy revealed multiple metastatic abscesses in all organs. Blood culture was positive. Microscopic examination of the abscess content showed branching yeast cells with surrounding mononuclear cell infiltration. No central necrosis or giant cells were seen. These findings are those of "first-degree virulence," according to Mackinnon,[10] who investigated the pathogenicity of *C. albicans.* (See also McKinney.[11])

Another rabbit weighing 2.5 kg. had a similar suspension injected into its right ureter, which had been ligated below the injection site. After fourteen days the rabbit, apparently in good health, was killed. Autopsy showed the right kidney to be pale and swollen. Yeast cells and inflammatory reactions could not definitely be demonstrated. The liver showed some foci of mononuclear infiltration. The blood culture was negative.

In summary, intravenous injection of yeast organisms caused septicemia with miliary dissemination of yeast cells, which were recoverable from the multiple abscesses. Kidney infection by ureteral injection was not successful.

DISCUSSION

The question arises as to whether this was a primary infection with *C. albicans,* or whether, as in some reported cases, the occurrence of the yeast was a secondary invasion. The excessive growth of the organism in the intestine, the allergic reactions, and the proved pathogenicity of the strain argue for an infection by the organism.

TABLE I. SKIN REACTIONS

NO. AND DATE OF TEST	PREPARATION USED	ORIGIN OF MATERIAL	METHOD OF APPLICATION	RESULT	CONTROLS
A. 12/13, 12/17, 1946	Extract I*	2-day-old culture of strain found in patient	Scarification	Negative	Two normal children reacted negatively.
B. 12/14, 12/18	Living yeast cells in suspension	2-day-old culture of strain found in patient	Scarification	After 24 hr., a round, raised wheal	Two normal children reacted negatively.
C. 12/15, 12/20,	Living yeast cells in suspension	2-day-old culture of strain found in patient	Intracutaneous injection	After 24 hr., a pustula .5 cm. in diameter with central necrotic area and dark red rim	Two normal children reacted negatively. In addition, injection into other arm with normal saline was negative.
D. 2/19, 1947	Living yeast cells in suspension	2-day-old culture of strain found in patient	Scarification	Became negative	Two normal children reacted negatively.
E. 2/15, 2/19	Extract I*	2-day-old culture of strain found in patient	Intracutaneous injection	After 6 hr. definitely positive	Two normal children reacted negatively. In addition, injection into other arm with normal saline was negative.
F. 3/7, 3/10	Extract I*	Culture of 4 other yeasts†	Scarification	Negative	Two normal children reacted negatively.
G. 3/13	Extract I* (stronger than previously	Culture of 4 other yeasts†	Scarification	Negative	Two normal children reacted negatively.
H. 3/24, 3/28	Extract I*	Culture of 3 yeasts‡	Scarification	Negative	Two normal children reacted negatively.
I. 5/11, 5/14	Extract I*	Culture of 4 other yeasts†	Intracutaneous injection	Negative	Two normal children reacted negatively. In addition, injection into other arm with normal saline was negative.
J. 6/2	Living yeast cells in suspension	2-day-old culture of strain found in patient	Scarification	Negative	Two normal children reacted negatively.

*Extract was prepared from actively dividing young cells according to Henderson. A colony of the culture was suspended in 5 c.c. normal saline plus 1 c.c. N/10 hydrochloric acid, boiled for ten minutes, centrifuged, and the supernatant fluid used after neutralization.

†The yeasts used were: *C. parapsilosis* (Ashford—Langeron and Talice); *C. krusei* (A. Castellani—Berkhout); *Torulopsis neoformans* (Sanfelice—Radaelli); *Saccharomyces cerevisiae* (Hansen).

‡The fungi used were: *Histoplasma capsulatum* (Darling); *Actinomyces innominatad* (Baldacei); and *Sporotrichum Beurmanni* (Matruch and Ramond).

From the studies of Owen[12] and others it is probable that infection with a yeast occurs only after sensitization, which can follow repeated invasions of a minor nature. The erythematosquamous skin lesions, which disappeared as the urine cleared, we interpret as a proof of sensitization. The scarification reactions, which became negative when the rash disappeared, also argue for an allergic state. The second and third intracutaneous injections reacted positively in shorter time, which argues for the formation of antibodies after the first injection.

SUMMARY

A case of generalized infection by the yeast *C. albicans* has been described, with localized infection of the left ureter, the bladder, the urethra, and the vulva. Infection of the lower bowel was also present, with symptoms resembling intussusception. At the same time, the lungs were abnormal, possibly due to an allergic reaction. Further arguments for this allergic state were found in the skin rash which was recognized as moniliid, and in the results of the skin reactions to antigen prepared in various ways (Table I). Animal inoculation showed the yeast organism to be pathogenic. Recovery was apparently spontaneous although several therapeutic measures were employed, including potassium iodide, a lactose diet, and alkalinization of the urine.

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TUBERCULOUS MENINGITIS TREATED WITH STREPTOMYCIN

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BECAUSE the use of streptomycin in tuberculosis is still in the experimental stage, we believe it will be of value to report in detail a case of tuberculous meningitis in a 7-year-old boy successfully treated with streptomycin and followed for one year.

Tuberculous meningitis has been described as the most frequent and the most hopeless type of meningitis occurring in infancy and childhood.[1] Approximately 65 per cent of children who succumb to tuberculosis die from tuberculous meningitis, and 90 per cent of cases of this disease occur in the first decade of life.[2-6]

Although prognosis is very poor, there are several cases reported in the literature in which the patients have recovered without the use of specific treatment. In 1931 Kramer and Stein[7] selected seventy-three cases which they considered to be authentic in a review of the literature. Cases of recovery since then have been reported by Jennings,[8] McQuinness,[9] Kelly,[10] Hobson,[11] and Parry.[12] Experience at Boston City Hospital over the past thirty-two years reveals uniform fatal termination in all cases of tuberculous meningitis. There have been 178 deaths in children, and all died on the average within seven days after admission to the hospital.

CASE REPORT

The patient, a 7-year-old boy, was admitted on Oct. 24, 1946, because of cough, fever, anorexia, and irritability of two weeks' duration. Approximately two years prior to entering Boston City Hospital he was treated at St. Elizabeth's Hospital in Brighton for tuberculous pleurisy with effusion involving the left lung. He remained in the hospital for two weeks and was then allowed to continue with bed rest and supportive therapy at home. There was no other previous serious illness.

On the day of admission the patient appeared irritable and listless, and his mother noted for the first time a weakness in the left arm. When seen by the family physician he was found to have nuchal rigidity, and admission was advised with the tentative diagnosis of tuberculous meningitis.

Examination revealed a well-developed but somewhat poorly nourished child. He appeared drowsy most of the time but was cooperative and well orientated. Besides the nuchal rigidity, there was a bilaterally positive Kernig's sign, a left facial weakness, and a paresis of the left arm and leg.

The temperature was 103° F., the pulse 100, and the respirations 20. The blood pressure was 100 systolic, 80 diastolic.

Examination of the blood revealed a red cell count of 4,500,000 with a hemoglobin of 80 per cent, and a white cell count of 15,700, the differential count being 46 per cent neutrophiles, 50 per cent lymphocytes, and 4 per cent monocytes. The urine gave a positive test for albumin and contained 10 to 20 red blood cells per high-power field. The spinal fluid on admission showed a normal pressure and had the appearance of ground glass, with 79 neutrophiles and 137 lymphocytes per cubic millimeter. The total protein was 51 mg. per cent, sugar 25 mg. per cent, and chlorides 617 mg. per cent. No pellicle formed on standing, and no acid-fast bacilli could be seen on smear. However, a guinea pig inoculation at this time was reported as positive for tuberculosis six weeks later. Chest x-rays revealed hila thickening and increased lung markings with a linear strand of thickened pleura at the right base. The Mantoux test was positive with 0.01 mg. of tuberculin.

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Although a diagnosis of tuberculous meningitis was made, no streptomycin was immediately available. Penicillin and sulfadiazine were administered prophylactically, but there was no fall in the temperature. On Nov. 1, 1946, the ninth hospital day and twenty-third day of illness, streptomycin therapy was started.

The patient was treated with streptomycin for a period of 141 days (almost five months), receiving a total of 70,458,332 units intramuscularly and 2,675,000 units intrathecally. At first, 83,333 units were given every four hours intramuscularly (0.5 Gm. daily) for forty-seven days. The dosage was then changed to 125,000 units every six hours (0.5 Gm. daily) for the patient's comfort, and was continued until the end of treatment. Intrathecally, he received 25,000 units daily for the first forty-three days, then 50,000 units every other day for seventeen days, and finally during the last eighty-two days he received 50,000 units twice a week.

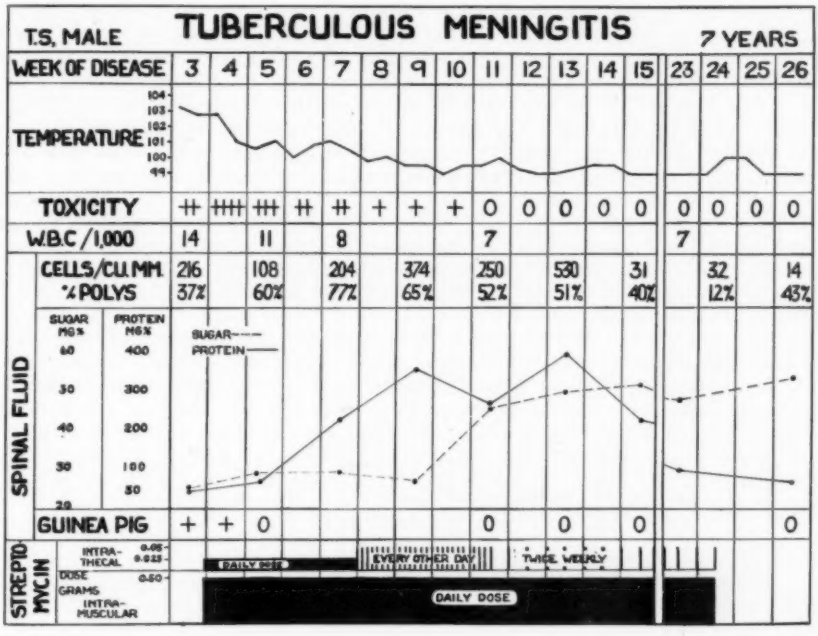

Fig. 1.

Following admission the patient's temperature remained between 102° and 103° F., but shortly after streptomycin therapy was instituted the temperature gradually began to fall, ranging between 99° and 102° F. After approximately three months of treatment his temperature remained normal. There was a daily rise to 100° F. for four days following cessation of treatment, although no cause could be found for this.

During the first three days of hospitalization the patient ate well and seemed to be fairly well orientated. His speech was somewhat incoherent, he was incontinent of urine and feces, and he slept much of the time. Gradually the patient began to fail, however, and by the tenth hospital day he had become

disorientated, extremely drowsy, and was unable to speak. When aroused he could be fed and would answer questions by nodding, but did not recognize members of his family. Although streptomycin therapy was instituted at this time, he did not struggle or cry when receiving the intramuscular injections or daily lumbar punctures. By the third week of treatment he began to use his right hand in feeding, appeared interested in his surroundings, and cried when the lumbar punctures were performed. On November 23 he spoke a few words for the first time in three weeks. Guinea pig inoculations of spinal fluid at this time were negative and remained so throughout the hospital course. Following this the patient slowly became more responsive and orientated. During his seventh week of hospitalization he responded to simple commands, could repeat words after the examiner, and could identify a few simple objects. There was no improvement in the left facial paralysis, and splinting and physiotherapy were required to prevent contracture deformities of the left arm and leg. Gradually the mental status improved, and by the ninth hospital week he seemed to be as bright and alert as any normal 7-year-old boy.

The spinal fluid sugar slowly rose to normal, as shown in Fig. 1. Between the eighth and thirteenth weeks there was an increase in the cells and a marked rise in total protein, and this may have represented a reaction to the streptomycin. Chest x-ray on December 5 revealed a hazy density in the right hila region, but by Feb. 12, 1947, the lung fields were completely normal.

During the last few weeks of treatment, physiotherapy was continued and gradual mobilization attempted. He was unable to use his left leg until the fifteenth week of treatment, and then only with the aid of a posterior splint. At the time of discharge he could walk quite well with the leg splinted, and although the left arm could be fully flexed and extended he could not grasp objects with his hand. A Stanford-Binet psychometric test administered shortly prior to discharge revealed an I. Q. of 105 and the level of intelligence was concluded to be "good average."

The patient was discharged on April 2, 1947. During the first few weeks at home he tended to stagger when walking. At present, one year from the onset of illness, he appears clinically well except for the persistence of his left facial weakness and left hemiparesis. The arm can be used, but the child is still unable to grasp with the fingers. The left leg drags slightly and has a "slapping" characteristic when walking or running. He has remained mentally alert and active, but at times is very irritable and restless. There has been no impairment of vision or hearing.

DISCUSSION

Although the boy whose case we have presented appears to be cured clinically, it cannot be stated with certainty that the tubercle bacilli have been completely eradicated.

The fact that streptomycin is the most effective antibacterial agent known for tuberculosis has been shown through experiments conducted by Hinshaw and Feldman and their co-workers.[13-16] Guinea pigs infected with virulent tubercle bacilli were treated with streptomycin. Although death was prevented, the action seemed to be suppressive rather than sterilizing, as tubercle bacilli were recovered from the spleen in a high percentage of cases. Hinshaw, Feldman, and their co-workers state that "streptomycin is most valuable in cases in which temporary suppression of the infection will enable the patient to gain the ascendency over his disease; healing then occurs by natural processes," and believe that streptomycin is indicated in the treatment of miliary tuberculosis and tuberculous meningitis.[13]

Recent cases of miliary tuberculosis in children treated and cured with streptomycin have been reported by Colby and Goettsch[17] and Sanford and O'Brien.[18]

The first detailed report on the use of streptomycin in tuberculous meningitis was by Cooke and associates[19] in the treatment of a one-year-old infant. A total of 15,049,000 units intramuscularly and 4,951,000 units intrathecally were administered over a period of sixty-eight days. At the time of writing the child was clinically well except for bilateral deafness and occasional periods of vomiting. Krafchik[20] has reported a case of a 15-month-old boy treated with streptomycin for fifty-seven days who obtained complete clinical recovery. He received a total of 24,000,000 units intramuscularly and 2,800,000 units intrathecally. Hinshaw and co-workers,[16] in their summary of 100 cases of tuberculosis in which the patients were treated with streptomycin, report on the results in nine cases of miliary tuberculosis and tuberculous meningitis. Of the four surviving patients only one was clinically well and asymptomatic. Reactivation of the disease had occurred in one, and residual neurological disturbances were present in the other three patients, including blindness and profound disturbances of cerebellar function. Treatment consisted of 100,000 to 200,000 units of streptomycin intrathecally daily for two to six weeks, and daily intramuscular injections of 2 to 3 million units for six months. None of the patients who died had received intrathecal therapy, and none of those who received intrathecal therapy had died. Other cases have recently been reported by Applebaum and Halkin,[21] and Mehas and Truax.[22]

In addition to the case reported here we have since used streptomycin in the treatment of four other children with tuberculous meningitis, two of whom are still living. One patient, a 2-year-old boy, was comatose on admission. Although he did not appear to improve with treatment he remained alive for eighteen days. The other patient who died was a one-year-old boy who had an associated miliary tuberculosis and died on the thirty-first day of treatment. The third patient is a 16-month-old girl who clinically and bacteriologically has recovered from tuberculosis, but is now partially blind and has marked cerebellar dysfunction. The most recent case is that of a 3-year-old Negro girl who has been discharged after 107 days of treatment and is clinically well except for a very slight right facial weakness. She received a total of 77,244,000 units of streptomycin intramuscularly and 1,625,000 units intrathecally.

SUMMARY

1. The case of a 7-year-old boy with tuberculous meningitis who has apparently been successfully treated with streptomycin is reported.

2. The reported cases of tuberculous meningitis treated with streptomycin have been reviewed.

3. Although results are variable, it is felt that early and intensive use of streptomycin intramuscularly and intrathecally may well favorably modify the course of tuberculous meningitis.

The authors wish to express their appreciation for the valuable assistance received from Dr. Thomas F. Paine in the treatment of the patient and the presentation of this paper.

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ADDENDUM

Since the writing of this paper, the 16-month-old baby and the 3-year-old Negro girl have both died. The former, who was clinically cured of the meningitis although cerebral damage was present, died following a gradual downhill course. Death occurred exactly thirteen months after admission, and an autopsy could not be obtained.

The 3-year-old girl, who was apparently almost completely cured, died just nine months after her first admission. She was well until two days before death, when she suddenly convulsed, became comatose, and developed a left hemiparesis. Autopsy revealed that death was due to a thrombosis of the right middle cerebral artery, which was surrounded by a large tuberculoma. This had caused infarctions in the right frontal and right parietal lobes. There was also an old infarct of the left internal capsule and putamen. Scattered tubercles were found in the mediastinal glands, liver, and spleen, from which acid-fast bacilli were found on smear.

TIME ELEMENT IN THE DEVELOPMENT OF IRREVERSIBLE BRONCHIECTASIS

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IT is generally known that bronchiectasis may be the result of infection behind a partial obstruction in a bronchus. As a result of the suppurative lobular pneumonia, the bronchial wall becomes necrotic with the eventual destruction of the musculoelastic coat. It has been thought that up to a certain point this pathologic process is reversible; for example, early relief of the obstruction to permit free drainage will allow the inflamed bronchus that is not as yet significantly damaged to heal with the restoration of practically normal bronchial structure. The point at which the process becomes irreversible and at which bronchiectasis is established is thought to be the time when a significant amount of necrosis has taken place in the musculoelastic coat of the bronchus or bronchiolus. There are only a few recorded cases in which an accurate determination can be made as to the length of this time.

Erb,[1] in his detailed report on "The Pathogenesis of Bronchiectasis," describes a case in which a 6-year-old girl died three weeks following aspiration of a tooth into a bronchus. Post-mortem examination at that early date revealed dilated bronchi with varying degrees of destruction of the musculoelastic coat. At that time there was no granulation tissue present. He also recorded a few cases in which the duration of time from the approximate onset of the infection to the time of death varied from four to six weeks. Erb divided the development of bronchiectasis into two periods—the stage of destruction, occurring in the first six weeks of infection, and the stage of repair, after six weeks had elapsed. The point at which the process becomes irreversible and bronchiectasis is established is thought to be the time when necrosis is found completely through the musculoelastic coat. The length of this time is influenced by many factors, such as the severity of infection, the degree of obstruction, the resistance of the patient and the virulence and number of organisms.

Because there are so few cases recorded in which it is possible to determine accurately the time of the onset of the infection, and because of the view held by some that bronchiectasis once established may be reversed, we are reporting a case in which there was a lapse of seven weeks from the onset of the obstruction until lobectomy demonstrated a well-developed and irreversible bronchiectasis.

CASE REPORT

C. B., a white boy 5 years old, was admitted to the Children's Surgical Service, Belleview Hospital, May 23, 1944, having been referred because of a foreign body (screw) in the right lung. His past history was irrelevant. He had never had any respiratory infection of consequence nor any other illness of importance. Until the onset of his present disability, he had been a normal, active, and healthy child.

On April 12, 1944, he aspirated a small screw which lodged in the right main bronchus. His mother realized immediately what had happened and took him without delay to a hospital in the vicinity of his home. Roentgen examination at this institution showed the screw in his right lung, and bronchospy was performed promptly.

From the Department of Pathology and from the Children's Surgical Service, Bellevue Hospital, New York.

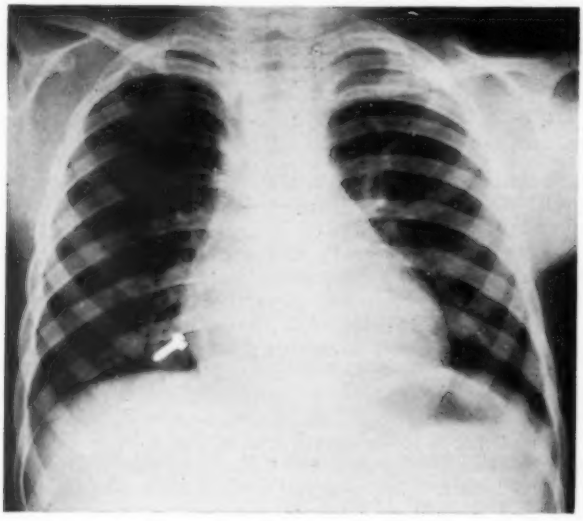

Fig. 1.

Fig. 2.

Figs. 1 and 2.—Posteroanterior and lateral roentgenograms showing location of screw.

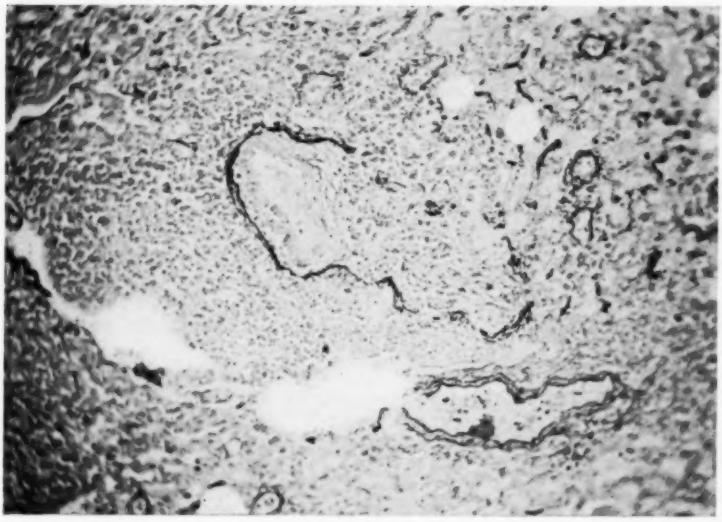

Fig. 3.—Photomicrograph ×150. Elastic and connective tissue stains showing disrupted and partially fragmented elastic tissue in wall of inflamed bronchiolus.

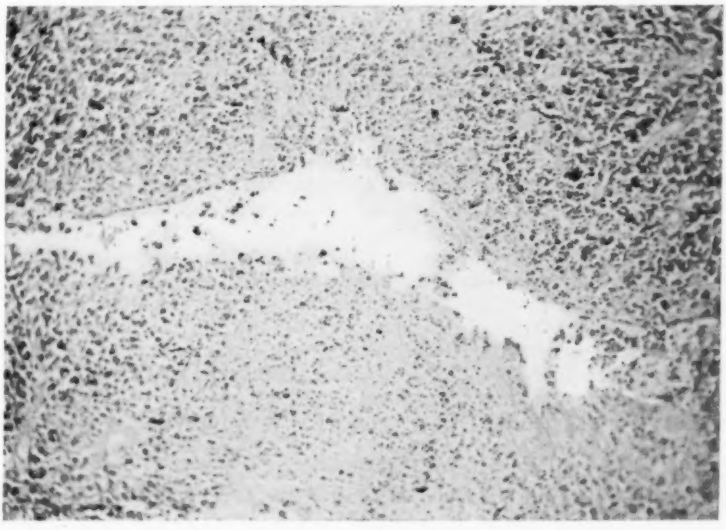

Fig. 4.—Photomicrograph ×150. Elastic and connective tissue stain showing complete absence of elastic tissue and complete necrosis of bronchiolar wall.

The screw was visualized in the right main bronchus, but attempts to remove it were unsuccessful. On the two successive days two more attempts were made, but they served only to wedge the screw tightly in the lower lobe bronchus from which it could not be extracted. Following the last attempt, severe respiratory obstruction developed, necessitating tracheotomy. This procedure relieved the obstruction, and in due course the tracheotomy tube was removed and the wound healed. Meanwhile, a cough developed which was productive of a small amount of mucus.

Upon admission to Bellevue Hospital, physical examination showed a well-nourished and developed boy of 5 years. He was coughing constantly and raising a moderate amount of whitish sputum but no blood. He was active and did not appear ill. Except for his lungs and the tracheotomy scar, no abnormalities were disclosed. Moderate dullness could be elicited over the base of the right lung, and a few coarse bubbling râles could be heard in this area. Roentgen examination showed a screw about 1.5 cm. in length in the right lower lung field (Figs. 1 and 2).

Lobectomy was performed June 2, 1944, fifty-one days after aspiration of the foreign body. The right sixth rib was resected and the seventh rib transected at its neck. The pleural cavity was entered through the bed of the sixth rib. The lower lobe was free and easily delivered, but the foreign body could not be palpated. The lobe was removed by the individual ligation technique and after removal was opened to demonstrate the foreign body. The wound was then closed to the emergence of a drain inserted through the resected sixth rib.

Convalescence was complicated by the development of empyema, from which *Streptococcus hemolyticus* was cultured. Sulfadiazine could not control the infection, and eventually the sinus tract had to be reopened. Bronchopleural fistula was never demonstrated, and later with the aid of penicillin, which had just then become available to us, the wound healed and the patient was discharged Nov. 18, 1944.

Description of Surgically Removed Lobe.—The pleura was smooth and glistening. The lung was subcrepitant. The site of the screw was indicated by several rust stains. The screw apparently had been embedded in the bronchus supplying the lower segment of the lobe. This segment was less crepitant than the remainder of the lobe. The bronchi in this segment were definitely dilated and in some instances were two to three times the normal caliber. Patchy areas of consolidation were present in the parenchyma surrounding these bronchi. The bronchial mucosa of the involved segment was reddened, granular, and ulcerated. The remainder of the lobe had a congested appearance; the bronchi and bronchioles were of normal caliber.

Histologic examination of sections through the involved segment revealed varying degrees of destruction of the bronchi and bronchioles. This destruction ranged from mild involvement of the mucosa and musculoelastic layer to complete necrosis. At some points there was beginning granulation tissue proliferation into the wall of the bronchi. In some areas inflammatory exudate in the alveoli was also undergoing organization. Elastic and connective tissue stain revealed that the elastic layer in places was completely destroyed and in other places partially fragmented (Figs. 3 and 4). This was also true of the muscle.

DISCUSSION

The early gross and histologic changes in the development of bronchiectasis have been adequately described by Erb.[1] Of interest, however, is the unusual degree of permanent damage to a large number of bronchi and bronchioles which developed in our patient in a period of such short duration as seven weeks. The fact that this process was present to such a degree is of even greater interest

when one realizes the patient was relatively symptom-free except for a cough during this period.

Fleischner[2] reported a case in which he claims the bronchiectasis was reversed to normal after being established for seven months. In view of Erb's detailed description and the findings in the case we have just reported, it seems unlikely that such an event could take place. The development of bronchiectasis is dependent to a great extent upon the destruction of the musculoelastic layer. Whether or not this destruction begins as a gradual ulceration through the mucosa or as a diffuse inflammatory process of the bronchial wall, is immaterial. The fact remains that once the elastic layer is destroyed, it is replaced permanently by fibrous tissue and can never be restored to normal. This process takes place within a rather short period of time. Thus it seems from a time basis and an anatomic basis that once bronchiectasis is established, the bronchiolar wall cannot be restored to normal.

SUMMARY

A case is presented in which the time for the development of bronchiectasis could be accurately estimated.

A study of this case indicates that the early destruction of the musculoelastic layer precludes the possibility of a reversibility of bronchiectasis.

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HOMOLOGOUS SERUM HEPATITIS

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THE improved availability of prepared plasma to the practitioner plus the the fact that its usage does not require blood typing or crossmatching has increased its popularity as a therapeutic agent. Because plasma is being used more freely, the hazard of its causing homologous serum hepatitis must not be overlooked.

Homologous serum hepatitis became a real problem to the armed services during the recent war and has received considerable attention and investigation. Whenever pooled blood, serum or plasma, is given parenterally there is the chance that it contains an agent, thought at present to be a virus,[1] which will cause hepatitis with or without jaundice. The severity of the hepatitis is not related to the size, route, or frequency of the injection.[2] Therefore, every time a parenteral injection of plasma or whole blood is given there is the risk of giving to the patient a potentially fatal infection in a definite percentage of cases.[3] The liver cells die from a coagulation necrosis.[1]

To help prevent such fatal potentialities it is recommended that no blood be taken from any donor who has received blood or plasma within the previous six months or who has had any so-called virus infection during that period of time. The incubation period of homologous serum hepatitis is from two to five months.[4-7]

The following is a case report of homologous serum hepatitis with encephalitis and anuria in a 3-year-old child subsequent to the intravenous injection of plasma.

On June 5, 1946, C. H. was in an automobile accident and sustained a compound, comminuted fracture of the right leg. He was immediately admitted to James Walker Hospital. On June 8 an open reduction was done and a metal plate was inserted. The patient went into shock on the operating table and was given 450 c.c. pooled plasma. Later that day he was given 350 c.c. intravenous glucose. He was started on a course of penicillin, 20,000 units every three hours.

On June 11 blood examination revealed: hemoglobin, 40 per cent; red blood cells, 1,820,000; white blood cells, 8,500; and polymorphonuclear cells, 56 per cent. On June 12 he was given 200 c.c. whole blood from his father. For the next seven days he ran a temperature ranging from 99° to 103° F. On June 17 the hemoglobin was 78 per cent; red blood cells, 4,050,000; white blood cells, 9,350; and polymorphonuclear cells, 53 per cent.

On July 8 he was again operated upon. The metal plate had slipped, and there was overriding of the bone ends. Screws were put into the metal plate. On this day and again on the following day he received 200 c.c. whole blood from a friend. Neither the friend nor the father had received blood or plasma or had had any virus infection during the preceding six months.

On August 6 the patient was discharged home in good condition.

On September 9 (three months after the injury and the reception of plasma) he developed a low-grade fever, malaise, and vomiting. At this time he was found to have hemoglobin of 82 per cent and white blood cells, 9,000.

On September 14 the child was admitted to Babies' Hospital with the complaint of fever and vomiting for five days, and jaundice, anuria, and stupor for one day. Stools remained normal in color.

From Babies' Hospital, Wilmington, N. C.

Physical examination revealed a fairly well-developed and nourished white male child aged 3 years, weighing 30 pounds, with generalized moderately jaundiced skin and sclerae. He was stuporous and appeared to be acutely ill. There was no lymphadenopathy. Ears, nose, and throat were negative. The heart had normal rate and rhythm with no murmurs. The lungs were clear. Liver, spleen, and kidneys were not palpable. There was slight nuchal rigidity. Reflexes were physiologic.

Laboratory Findings.—On admission the urine was negative for albumin, sugar, and urobilinogen, the specific gravity was 1.014. Bile (methylene blue test) was positive as was the test for acetone. Urine on the eighth hospital day was negative for bile. Urine culture on the fourth hospital day was sterile. Stool specimens were repeatedly negative for ova and parasites. Spinal fluid on admission was clear with 13 cells per cubic millimeter and with slight increase in globulin. A qualitative van den Bergh test on the second day gave a biphasic direct reaction. Total blood protein on the second day was 5.15 Gm. Blood was Rh-positive, Type A.

TABLE I. BLOOD EXAMINATIONS

HOSPITAL DAY	HEMOGLOBIN (%)	R.B.C.	W.B.C.	POLYMORPHONUCLEARS (%)	LYMPHOCYTES (%)	EOSINOPHILES (%)	BASOPHILES (%)
Admission	80	4.9	17,800	70	30	2	
2	77	3.7	16,100	50	48	1	1
8	73	3.9	9,800	80	48		
13	88	4.7	10,800				

Hospital Course.—On admission the boy was irrational. He groaned and was very restless and voided involuntarily. The first five days in the hospital he remained stuporous and was given intravenous glucose once or twice daily. Other therapy was symptomatic only.

By the sixth hospital day he was talking coherently, was playful, and able to sit up in bed. On the seventh day his jaundice was noticeably decreased, the liver was palpable two fingerbreadths below the costal margin, and the abdomen was distended. On the ninth day he had a fluid wave, shifting dullness, and pitting edema of the legs.

On the eleventh and twelfth days he received two whole blood transfusions of 200 c.c. each, the friend again being the donor. This treatment was given to correct a fall in the hemoglobin and red blood count.

Throughout his hospital course the boy had an evening rise of temperature to 100°-101.6° F. He was discharged from the hospital on the thirteenth day (September 26) in an improved condition. The jaundice, ascites, and edema disappeared one week after he left the hospital.

With the exception of recurring tonsillitis he has been well since this episode, has gained weight, and has been symptom-free.

SUMMARY

A case report of homologous serum hepatitis in a 3-year-old child which occurred three months after parenteral injection of pooled plasma has been presented. The patient also had encephalitis and anuria as complications of the hepatitis. This case is reported to stress the fatal potentialities of pooled human blood products and the importance of using no donor who has received blood or plasma or has had any so-called virus infection during the preceding six months.

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Medical Care

THE TREATMENT OF COMMON RESPIRATORY INFECTIONS

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THE answers to questions involving the diagnosis and treatment of common respiratory infections in examinations given by the National Board and by the New York State Board of Medical Examiners have suggested this review of the subject. Common colds and their complications comprise the greater part of medical practice, adult as well as pediatric, and it would seem that candidates for licensure should have a reasonable amount of knowledge about the recognition and care of such infections, but this does not seem to be the case. Questions which describe a case of simple acute pharyngitis or tonsillitis are regularly missed by overshooting the mark, and diagnoses of poliomyelitis, diphtheria, meningitis, or almost any more serious disease are made by about three-fourths of the candidates. The answers on treatment are equally absurd. Admitting the patient to a hospital, ordering elaborate diagnostic procedures, laboratory tests, and heroic treatment, seems to be the only plan which occurs to most candidates.

The practicing physician is not free from guilt in this direction. I see many patients in consultation whose parents have been subjected to great and needless expense, as well as to undue anxiety. For example, a child with an acute pharyngitis, or "grippe" with a red throat, is treated with sulfonamides for two or three days. If the fever does not yield promptly, as it often does not, especially when the general care of the child has been neglected, the patient is rushed to the hospital. Penicillin intramuscularly is usually started at once and given every few hours, the pain disturbing the child's rest. Orders are given for complete blood counts and cultures, urinalysis, x-rays of chest, lumbar puncture, throat cultures, etc., etc. The parents eagerly wait the results of the many tests. Before they are all reported the patient is usually convalescent, for the four-day fever has run its normal course, in spite of the treatment! When the hospital bill is rendered, the shock to the parents does not endear the physician to them. The small child is often left in a nervous and unsettled state from being taken out of his familiar home into the hospital, where strangers do painful things to him, mostly unnecessary, and where he is often neglected in essential matters.

For the reasons just given a discussion of the care of colds and their complications seems justified. It cannot cover the diagnosis of all the respiratory infections, but it must be pointed out that simple rhinitis, sinusitis, acute pharyngitis, follicular tonsillitis, otitis, laryngitis, tracheitis, and bronchitis comprise the largest part of acute illness in childhood. One should be able to make a diagnosis of the site of the respiratory infection from a careful analysis of the symptoms and a thorough examination for physical signs, or lack of them.

I have always been annoyed by the blanket diagnosis of "upper respiratory infection," which is applied to *all* acute respiratory disease by students, interns, and practitioners—even when the only physical signs are râles at the base of the lungs.

The treatment of all these conditions may be divided into general and special measures. Every acutely ill child needs care as a sick child, not just as a case of a disease. The patient is often forgotten in ordering drugs or antibiotics, yet the child's recovery depends more on his nursing care than on the drugs given him. It is the physician's duty to instruct the mother or nurse in the simple things which promote the child's comfort, increase resistance, and hasten recovery. Too often he takes the general care and nursing for granted, or perhaps wearies of repeating it to every mother, or omits it because it has never occurred to him that such matters are important to the patient or of concern to the physician.

GENERAL TREATMENT

Rest is needed by every sick child. Freedom from muscular activity, changing temperatures, and nervous strain relieves the vital forces of the body and allows them to be devoted to building up resistance to infection. It is the habit of some physicians to allow children to be up and out of doors with a cold if they have no fever. Mothers are astonished when a child with a cold is ordered to be put to bed when the sun is shining outside. It is my experience that the child who goes out with a little cold too often comes back with a bad one, an otitis, or even a pneumonia. Children who are put to bed promptly at the onset of a cold usually have a milder infection, fewer complications, and a more prompt recovery. Rest, however, does not mean that the child must lie flat in bed with nothing to amuse him. He may sit up in bed, on a couch, or even in a big chair if he is properly dressed and covered. His clothing should be adequate but not too heavy. His legs, which are under the bedding, need only one layer, a nightgown or pajamas. His trunk and arms need somewhat more—either a shirt under his night garment or a light robe or sweater over it. But when he lies down to sleep one layer is sufficient, for a shirt under the night garment, makes him too hot and he is likely to throw off the bedding and then become chilled. The bedding should not be too heavy. I have seen many a child with high fever (104° to 105° F. or more) covered with shirt, night garment, sweater, or bathrobe, and four to five blankets. It has been shown that the temperature of healthy children can be raised several degrees by bundling of this sort. This matter definitely concerns the doctor, and he should not forget it.

The child in bed must be amused. Mothers frequently say: "That child will not stay in bed." Of course he will not lie flat without occupation unless he is too prostrated to hold up his head. A sick child needs more attention in this direction than a well one. First he must be made comfortable with pillows or back rest. A bed table or lap board is of great help because it gives him something to play on, a focus for his attention which helps to keep him quiet. He must have small toys with which he can play on his lap, not large motor vehicles which go on the floor. New toys, books, crayons, sewing—all the endless small occupations which entertain the child—must be provided, a new one

every few minutes in all probability, for the sick child's attention lags easily. A "wonder bag" is an old standby: a large paper bag with many small toys, old and new in it, from which the child can take out one thing at a time. Toys in boxes, one to be opened every hour, may divert him. Play should not be too continuous if fever is present, but broken by rest periods at intervals. Radio music of the softer kind may be quieting, but not loud jazz, and selected programs, not crime features nor exciting soap operas.

The sick room should be kept at a temperature not over 68° to 70° F. Most houses, except those of the better class, are kept too hot. It is not uncommon to find a sick child, overbundled in bed, in a room at 85° to 90° F., the relatives "keeping him good and warm" because he is sick. The mother often is dressed for midsummer, in a cotton dress with bare arms and legs, but the poor little child is sweating in the Turkish bath temperature. The mother must be instructed to keep the room cool and to put on more clothing if she is chilly. Except in the coldest weather, radiators and registers in the sick room should be turned off and the room warmed through open doors. A steam radiator will overheat almost any room if left on longer than a few minutes at a time. The air in these hot rooms is, of course, relatively dry, for the need for moisture in the air rises rapidly with each degree of temperature. If fresh outside air is admitted, it is not always necessary to provide extra moisture. It does no harm to add it to the air, and this may be desirable in some cases. An electric stove with a pan of boiling water, or a wet Turkish towel on the radiator while it is turned on, will evaporate a large amount of water in a short time. The usual small "vaporizer," which holds only a few ounces of water, is a futile gesture, not worth its cost. I am skeptical about the value of steam, medicated or otherwise, in most respiratory diseases. If the room is kept cool and the air fresh, there is usually enough moisture. That fresh air is needed in every sick room almost goes without saying, but the method of supplying it depends on many factors—the season, the outdoor temperature, the direction of the wind, and the position of the bed and windows. In mild seasons windows may be kept wide open, but in winter a small crack may suffice, especially with a windward window. In bitter weather the window may be opened wide for a few minutes every hour or two, the child being covered warmly meanwhile. New air must be supplied effectively. The mother who opens the window a small distance at the top and then covers it with a drawn roller shade is fooling herself but not the open-eyed physician.

Bathing is needed more by the sick child than by the well one. There is usually considerable perspiration in bed, insensible or obvious, due to the fever, antipyretics, and often by overcovering. The fear of bathing during a cold is quite ungrounded. A child may safely have a quick tub, not too warm and *not* in an overheated bathroom, for he may be chilled on returning to a cooler room. Sponge baths are more chilling, more work, and less efficient. Sponging may well be reserved for reducing temperature in hyperpyrexia, although with a small child, who can easily be carried to the bathroom, a lukewarm tub will accomplish the result even better and much more easily.

The planning of treatment of acute illness so as to do all that is necessary, spare the mother's time, and disturb the child as little as possible is something that never enters the head of the general run of physicians. Witness the order sheet for almost any acutely ill patient in any hospital. Temperatures are taken every four hours; nourishment is given at the nurses' convenience; drugs or injections are given every three hours, and nose drops or other treatments every hour or two. I once saw in consultation a child moderately ill with pneumonia who was having thirteen different things done to him at intervals of from one to four hours. Three nurses were kept busy, but the poor little fellow was given no time to sleep! Many such incidents could be cited. The plan of treatment should be laid out with care to avoid such errors. The best plan is to order the mother to do everything which must be done at one time, and then let the child alone to play or rest until the next series of treatments. The traditional four-hour interval is not the best one, for it allows only four feedings in the daytime and it is often desirable to give five. The three-hour interval (7-10-1-4-7) is a better solution, for it gives five feedings and treatments in twelve hours. If necessary, one or more may be given at night. The mother or nurse should go through a definite sequence at each three-hour period. The best one seems to be as follows: Take temperature, feed, give medicine and treatments; then let alone or amuse until three hours have passed. Water may be given during the interval. My associates and I have found useful a printed order sheet for acute illness. It may be modified for individual cases. Exact hours for food, medicine, and treatments are always written. Bathing may be done between temperature-taking and feeding. (See Fig. 1.)

A plan like this makes the care of the patient much easier for the mother. She can plan her day, attend to her duties, or even rest, if the child does, until the next three hours are past. The physician who orders medicines, treatments, food, and temperature taking at all sorts of intervals should be compelled to stay with the patient for twenty-four hours and try to carry out his own orders.

The feeding of the sick child is more easily planned on the three-hour schedule than on any other. This feeding should definitely be prescribed as to quality and quantity as well as intervals. The sick child, especially one with fever, has a diminished digestive capacity, as shown by his anorexia, and by the results if too much food is given, since vomiting often occurs. The hydrochloric acid of the gastric juice is much diminished with the onset of fever. The child, therefore, cannot easily digest certain foods, and chief of these is milk, which is the heartiest food he gets. Large and tough milk curds are often more than the stomach can handle, and are returned more or less promptly in evidence of the fact. Homogenized milk is tolerated but little better. The sick child needs three things: water, carbohydrate, and alkali. He does not need much protein or fat, and vitamins can be disregarded in brief illnesses. Therefore the diet in illness should contain starchy foods—cereal, bread (preferably toasted), sugar (in moderation), and potato. These give him carbohydrates to prevent acidosis. Fruit juices supply alkalis (citric acid yielding bicarbonate), some calories in their sugar, water, and ascorbic acid for good measure. Other liquids may be added, such as broths or vegetable juices for variety. Palatable desserts,

such as cornstarch puddings, gelatin, applesauce, and ice cream, may be given to tempt the child to take calories and carbohydrates. The small amount of milk in some of these will do less harm than milk taken plain, since the curds will be smaller. It is a shock to many students, nurses, and even physicians to learn that a milk diet is not the first thought in illness. Many years ago I was appointed a visiting physician to a hospital for infectious diseases. There were several severe cases of scarlatina with high fever, the children toxic and prostrated and on a pure milk diet. The custom was to give only milk till the fever was gone, then add cereals. When I ordered the sequence reversed, the institution was rocked to its foundations. It must be repeated that the exact kind of food, the amount of it, and the hour at which it is to be given must be written plainly and in full. It is wise to alternate carbohydrate foods with orangeade. As the fever leaves, more milk may be added, and then eggs, meat, and vegetables during convalescence.

The Bowels. A daily evacuation is even more important for the child in sickness than in health. This matter is one which is regularly neglected by the physician, judged by patients seen in consultation and in hospitals. He may order a cathartic or an enema early in an illness, but too often forgets to give further instruction thereafter. A day or two with no bowel movement results in higher fever, more anorexia, a coated tongue, bad breath, and delayed recovery. The child who is seen at the onset of an illness should have an enema at once, unless the mother is sure that there has been an adequate evacuation that day. A soapsuds enema is the quickest, easiest, and surest method of emptying the lower bowel. To an infant this may be given with a 4-ounce infant's syringe, but one bulbful may not be enough. Sometimes it is necessary to give several to make the bowels move adequately. One bulbful which produces no result is a mere gesture, not an enema! Older children need more liquid, up to a pint or more, and the fountain syringe is the easiest way to give it. After the initial emptying of the bowel, one should take thought for the morrow. Enemas are a nuisance to mother and child, and one may well avoid them when possible. A mild laxative should be given each night to a sick child unless there is diarrhea. He will be inactive and on a low diet, and the chances of a normal morning movement without help are slim indeed.

The laxative of choice is the one which the mother has found useful in the past, the one which the child will take, and the one which works. If the child has never had a laxative, the physician's choice is free. Like all medicines given children, the laxative should be as palatable as possible. Milk of magnesia straight, in orange juice, or in milk, is most frequently used. Infants and young children take it well, and it is usually effectual. An infant needs ½ to one teaspoonful, an older child 2 to 4 teaspoonfuls or more. The mother usually knows the dose required. Older children may object strongly to the somewhat bitter taste, so another laxative must be sought. The aromatic fluid extract of cascara is a good laxative, but the bitter taste is poorly disguised and many children refuse it after the first dose. The plain fluid extract is much worse and should never be ordered. Various syrups containing senna are palatable and effectual. Syrup of senna, U.S.P., may be used, but in the family medicine

cabinet Castoria or Syrup of Figs is usually found. If the child will take either one, and if it has been effectual in the past, we may close our eyes to the fact that these are proprietaries. Phenolphthalein in flavored tablets or in chewing gum is a good laxative when it works, but is not effectual with all children. Salines are more or less unpleasant to taste. The carbonated solution of magnesium citrate is the only pleasant one, but many children object to carbonated drinks, and the dose is bulky. Bicarbonate of soda is the simplest and one of the best salines but one which is rarely used; indeed, many do not realize that it acts as a laxative. Like all salines it should be given first thing in the morning, half an hour before food, and in a very cold solution. One-half to one teaspoonful dissolved in 4 ounces of water, which is then iced, makes a solution not too unpalatable, which older children may take. Of the other salines, Rochelle salt (sodium and potassium tartrate) is least unpleasant. In some instances a laxative like phenolphthalein may be given at night followed by a small dose of sodium bicarbonate next morning. This combination is useful in children who fight enemas too much and with whom laxatives do not work well. Sugar-coated pills may be given older children but obviously have no place in the treatment of young ones, who may chew them and get the bitter taste. Mineral oil, plain or in emulsion, is useful in chronic constipation but is not reliable in acute illness where something stronger is needed.

Certain symptoms make the patient so uncomfortable that they demand treatment.

Fever is probably not altogether undesirable, for it is nature's method of fighting infection. Nevertheless it makes the patient restless and uncomfortable, causes muscular aches and pains, and may disturb sleep. High fever in itself may become dangerous, especially to the child who has the tendency to convulsions. It is justifiable to try to keep the fever from becoming too high, even though we know we are not curing the patient by merely reducing it temporarily.

Aspirin is the drug most often used and it works well, except in the rare cases of idiosyncrasy. The dose need not be large. The rule of giving drugs by weight works for almost all drugs, and aspirin is no exception. For example, an adult will take 10 gr. to relieve the symptoms of fever. If we consider the average adult's weight as 150 pounds, then the dose per pound for a child is $^{10}/_{150}$ or $1/15$ gr. The doses commonly given will approximate this very closely. All tablets should be crushed and given with sugar and water from a spoon. They may be mixed with honey, jelly, applesauce, or even concealed in a small chocolate drop as a last resort. Aspirin may be repeated safely every three hours if the temperature is over 102° F.

Hydrotherapy is useful in reducing fever, but it is often ordered and administered unwisely. Cold sponges or alcohol sponges are resented bitterly by many children and are uneasy and troublesome to give. A tub bath is much easier, just as effectual, and the child is accustomed to it. The water need be little if any cooler than the usual bath, for with the higher temperature of the child a bath at 98° to 100° F. is enough below his body temperature to be an effectual means of reducing it. The warm bath brings blood to the surface, from

which it is often driven in fever by spasm of the peripheral vessels, and so lets the body radiate heat. The cold sponge bath merely chills the surface further, and its actual cooling capacity does not make up for this fact. The drop in body temperature after a warm bath is often greater than from a cold sponge. Infants and young children are easily carried to the bathroom, and older children can usually walk there, except in grave illness when it is, of course, necessary to use a bed bath. Care must be taken not to overheat the bathroom during the bath, which is bad for both patient and nurse. Aspirin may be enough when the temperature reaches 102° or 103° F., but when it is 105° F. or more both aspirin and hydrotherapy should be given in order to reduce the fever promptly. We must not forget the possibility of a convulsion from hyperpyrexia.

Pain is associated with fever (general aching) or with complications, such as otitis frequently, and pleurisy less often. Aspirin is adequate for the muscular pains of fever but is not enough for severe pain. Phenacetin (acetphenetidin) is the best of the coal tar analgesics, although it has apparently been forgotten by many medical schools. Pyramidon had supplaced it almost entirely until the dangerous effect on the bone marrow was discovered. Phenacetin has little effect on bone marrow, has little taste, and is effectual in relieving pain. Its dose is about the same as aspirin, roughly $^1/_{15}$ gr. per pound. It may be combined with aspirin or with other analgesics.

Codeine is the best of the morphine derivatives for pain in childhood, but the dosage ordinarily used is too small. It should be calculated on the basis of a real pain-relieving dose in an adult, which is a full 2 gr. This gives $^2/_{150}$ gr. or $^1/_{75}$ gr. per pound for the child. At 15 pounds the dose is then $^1/_5$ gr., at 25 pounds $^1/_3$ gr., and at 50 pounds $^2/_3$ gr. One sees a dose of $^1/_4$ gr. ordered for a large child with no relief from pain. For an acute earache the combination of codeine and phenacetin is most useful. If a child is subject to earache with every cold, the mother should have on hand powders containing phenacetin 1 to 3 gr., codeine sulfate $^1/_4$ to $^1/_2$ gr., sugar 10 gr.

Restlessness and inability to sleep are frequent and important symptoms of acute respiratory disease needing attention. They may be due to nasal obstruction, to cough, to pain in throat, ear, or pleura, or merely to the general discomfort of fever. In any case the child is entitled to his sleep, for lack of it lowers his resistance. Furthermore, the parents need their rest. A mother who is up many times a night is likely to acquire a cold herself from fatigue and chilling, as well as from contact with her child's infection, and a sick mother is no help in the problem. We must not forget the father, who has to support the family, for if he gets sick, economic strain or even disaster may result.

It may be that treatment of the obstructed nose and relief of the cough or pain may allow the child to sleep, but if he is still restless the mother should be prepared to meet the situation. She should have a sedative on hand with instructions to use it if needed, rather than to wait until midnight or later, when drugstores are closed and the doctor should be asleep. The pediatrician needs only a few drugs in the sedative group. Phenobarbital is the best and most often used. The doses prescribed are often too small, for children are quite tolerant of the drug. The dose may be calculated on the basis of weight. A full hypnotic

dose for an adult is 3 to 4 gr. A child will take 1/50 to 1/40 gr. per pound. Young infants tolerate 1/4 gr., and in the second year 1/2 gr. is not too much, but 1/4 gr. is not enough for a husky 2-year-old. Even larger doses than these may be needed and are well tolerated. Some children are affected so little by phenobarbital that some other drug must be used. For many years I have relied on carbromal (Adalin; bromdiethylacetylurea). This remedy is apparently not stressed in most medical schools, for I have rarely met a physician who uses it and many druggists do not keep it in stock. It is safe, quite efficacious, and leaves the patient (from my personal experience) with less of a "head" than the barbiturates. The full dose for an adult is 10 gr., so a child may take 1/15 gr. per pound. Most children to whom I have given it sleep well one or two nights and are relaxed and quiet next day. I have seen no bad effects. It is also useful for a nervous, jittery child after an accident, operation, or any unusual upsetting experience.

When a child is vomiting incessantly, or after a convulsion, or where heroic sedation is indicated, sodium amytal in suppository or even intravenously is useful. The dose by rectum may be about that of phenobarbital.

Nasal obstruction from swollen turbinates and discharge demands attention. We cannot stop the inflammatory process, but we can relieve the discomfort and diminish the dangers of some of the complications. Obstruction increases the likelihood of the development of sinusitis and otitis media. The list of agents which shrink the nasal mucosa is long. Many manufacturers produce them, a new one every year. Adrenalin and ephedrine have been followed by other substances which are said to give less local irritation and secondary reaction. The fashionable ones today are neosynephrin and Privine, although others may be as good. Solutions and jellies each have their advocates, and patients have their favorites. Jellies have certain advantages over drops. They stay in the nose longer and hence give a more prolonged action. Drops run through the nose so fast that their action is brief, unless care is taken in their administration. In using nasal jelly the tip of the tube containing the jelly should not be inserted into the nose, for it may hurt the child and the mother cannot see the amount administered. The tip should be kept outside the nostril and a drop of jelly just large enough to fill the nostril should be squeezed out. The child's mouth should then be closed by pushing up the jaw or holding the lips, preferably at the end of an expiration or cry. The resulting deep inspiration will then draw the jelly well into the nose. Older children will snuff it up voluntarily. Given in this way, few children will object to the jelly, although the mother often claims that it has been fought bitterly in the past. It is amusing to see her chagrin when the proper method is demonstrated and the child makes no objection. If drops are used, the child's head should be held in the inverted position, hanging down over the mother's lap or the edge of the bed. This position should be maintained for three to five minutes so that gravity can carry the solution to the upper and the middle meatus. When the head is upright or the chin merely elevated, the solution runs down the floor of the inferior meatus into the nasopharynx and may never touch the turbinates. Silver preparations (argyrol, neosilvol) may be used for children whose nasal dis-

charge is purulent or turbid. The indiscriminate use of these preparations in all cases of coryza is not necessary. The danger of argyria from long-continued use must not be forgotten, and mothers should always be warned not to use silver salts more than a few days at a time.

Cough in itself is not altogether a serious symptom, for by it the child clears accumulated mucus from the air passages, and it is not desirable to suppress it entirely. However, cough can be so frequent and severe that the child rasps his mucous membranes unduly, and so provokes further irritation. It is well to keep coughing under control. Cough can originate in any part of the respiratory tract, from the tickle of nasal mucus to that of a deep-seated bronchitis. We can judge the cause of cough by its character and by the physical signs, or lack of them, as in acute tracheitis. The cough from nasal mucus or from a dry pharynx merely needs treatment of the nose and throat. When it arises lower down it is usually necessary to give some cough medicine, partly as a placebo to the parent. Cough remedies are numerous, many of them worthless, most of them mildly effectual, none of them perfect. Some of the older ones, like Stokes' Mixture or those containing ammonium chloride, are unpalatable or nauseating. Of all the "expectorants," ipecac seems to be the only one which is worth using. In emetic doses it certainly increases the flow of mucus, but whether small doses alter the quality of the mucus or influence the inflammation of the bronchial mucosa is a matter of dispute. It does no harm at least, in small doses, and seems to do some good. Infants will tolerate 1 to 2 drops every three hours and older children up to 5 drops, but some children vomit with these doses and the amount must be reduced. Most cough mixtures contain codeine, and this drug certainly diminishes the irritation of a too-frequent cough. The great majority of medical graduates know only one cough medicine, codeine with elixir of terpin hydrate. I believe that the latter is worthless and that we ought to be able to write a better prescription. For a good many years I have used and taught the use of the following mixture. Many of my students agree that it is as good as any:

			Approximately	
℞	Codeinae Sulfatis	gr. v	0	3
	Syr. Ipecac.	ʒ ii	7	5
	Tr. Persionis	ʒ i	3	0
	Syr. Tolutani	q.s. ad ℥ vi	180	0

M. et Sig: One teaspoonful every 3 hours (after food).

This gives a dose of about ¼ gr. of codeine per teaspoonful. (Note: There are only six average teaspoonfuls in one ounce, *not eight,* or 5 c.c. to a teaspoon, not 4 c.c.) The amounts may be varied for age, or fractions of teaspoonfuls may be given to a younger child. The tincture of cudbear (persionis) is merely a coloring substance, deliberately put into all codeine mixtures. Its color makes certain that the mother will know what she is giving, and she can tell the physician that she needs more "red medicine." The point may seem trivial to the pure scientist, but to the practitioner it is one of importance. Syrup of tolu is said to have some expectorant properties. Other flavors may be more pleasing, such as syrup of orange, lemon, or wild cherry. In many instances an adjuvant to

the codeine, such as an antispasmodic, may be wanted. Antipyrine is useful for this purpose, and moreover is analgesic and antipyretic. It has the advantage of being the only water-soluble coal tar analgesic. One grain, more or less, per dose may be added to the previous mixture, usually 15 to 30 gr. to the 6 ounces.

Another ancient and time-honored cough medicine is the mistura glycyrrhizae composita, or Brown Mixture. While this is an old shotgun, it has some uses still. In the first place, it can be bought over the counter by the mother, on telephone advice, without the delay of getting a prescription and having it filled. Second, it is palatable and harmless. It contains little opium (approximately $\frac{1}{25}$ gr. per teaspoonful). The potassium and antimony tartrate is said to be an expectorant. The other ingredients are inert. I often suggest adding a drop or two of syrup of ipecac to a dose. But I suspect the greatest value of Brown Mixture is as a placebo, so that the mother who demands a cough mixture will be satisfied and the infant not harmed. It is safe enough to give small infants 10 to 30 drops and older children 1 to 2 teaspoonfuls. The amounts printed on the labels of bottles sold over the counter are too small.

One other drug useful in persistent or chronic cough is potassium iodide. This was an ingredient of all the old shotgun mixtures, but is rarely used for children. It certainly changes the character of expectoration, making it thinner and less sticky, and it is occasionally useful. It is usually prescribed in essence of pepsin or in an elixir, to be taken in milk. Ammonium chloride should not be given on account of its bad taste and doubtful value. The rest of the expectorants act more or less like ipecac and are not as good.

Among other means of stopping an irritating cough is warmth over the trachea, from a warm-water bag or a piece of flannel or woolen cloth around the neck. Hot or cold wet applications and counterirritants are not necessary. Cough lozenges are often useful to allay a cough from a tickling throat. Their value comes mainly from the sugar, although the menthol in some of them may help. Local applications to the chest may have some value. Camphorated oil and mustard are traditional remedies. If mustard is used it must be watched carefully or the skin may be burned. A thickish paste of mustard, 1 part, plus flour, 6 to 8 parts, wet with cool water, not hot, spread on cotton cloth, may be left on for three to five minutes but not much longer. Most mothers apply counterirritants to the sternal region. If used at all, they should be applied to the lateral and posterior parts of the chest. Their action, if any, must be purely a reflex one by stimulating the skin nerves, and there is no excuse for using counterirritation, except possibly in a deep-seated bronchitis.

Croup is a symptom which demands prompt attention. There is nothing so terrifying to a mother as to have her child waken choking and struggling for breath (almost always between 11 P.M. and 1 A.M.). Nothing gives such prompt relief as an emetic, and syrup of ipecac is the best and the most palatable. It is wise to have a fresh bottle of it in the patient's house in the winter months, especially if the child is prone to attacks, for drugstores are usually closed during the croup hours. (It is also a great help to have it handy when a child swallows poisonous substances.) The doses of ipecac on printed labels are often too small:

"five drops every fifteen minutes till vomiting occurs." We want prompt emesis, and there is no overdose of ipecac. It should be given in teaspoonful doses, repeated just as fast as the child can take it. My favorite method of impressing this matter is to tell the mother to give it until the teaspoonful going down meets the one coming up. Vomiting usually relieves the spasm of the glottis, and the child breathes more easily. Ipecac should be given in smaller doses for a few days, usually with codeine as previously described, to prevent the recurrence of croup a second or third night. It is well to waken the child at 9:30 or 10 P.M. the second and third night to give cough medicine and water, which prevent the drying of the laryngeal mucus into crusts, the real cause of the spasm. External dry warmth over the trachea is especially helpful in croup. Wet compresses are no better and are more trouble. The traditional croup kettle for steam inhalation is much overrated. Croup tents give too much steam and are too hot. Many children have been burned by the steam, and beds have been set on fire with alcohol lamps. The latter also may give off formalin vapor, which is decidedly undesirable. An open pan of boiling water in the room does no harm and placates the parent at least. Steam inhalations are impracticable for children and of doubtful value, since the steam hardly reaches the vocal cords at best.

Bronchospasm accompanies many cases of bronchitis, as well as true bronchial asthma. The latter is an allergic phenomenon primarily and cannot be discussed here, but there are many children who occasionally have more or less severe attacks of spasm of the small bronchi with ordinary bronchitis. There may be an allergic factor in these children, but they do not belong in the same group as chronic or seasonal asthmatics. The amount of discomfort caused by bronchospasm varies greatly. Some children are most uncomfortable from the dyspnea produced, but others, especially infants, seem to mind it very little. The spasm can be relieved by adrenalin solution 1:1,000 intramuscularly, but it is wise to give small doses at first until the susceptibility of the patient to the drug is ascertained. One to three minims (0.065 to 0.2 c.c.) is enough to relieve many patients, while 10 minims (0.6 c.c.) may give distressing cardiac symptoms. Adrenalin in oil may be used for a more prolonged effect.

Theophylline or aminophylline will relieve many patients as effectually as adrenalin. They may be given by mouth or by rectum and are often combined with phenobarbital to counteract the caffeinelike effect which makes the patient wakeful and restless. They often cause vomiting even when given by rectum. (Sodium amytal may be given by rectum to control the vomiting.) The patient who is subject to attacks of bronchospasm does not have to wait for the doctor's visit, if a supply of tablets or suppositories of these drugs is kept in the house. They have the advantage of sparing the child the pain of an intramuscular injection. Benadryl and Pyribenzamine relieve the nasal obstruction of allergic rhinitis, but I have seen little or no effect on bronchospasm.

Otitis media is such a frequent complication of colds that it deserves brief consideration. The first indication is to relieve pain with phenacetin or codeine or both. External warmth may help. Thorough shrinking of the nasal mucosa

should be prompt, for only by decreasing congestion in the nose and nasopharynx can the ear be drained through the eustachian tube. Antibiotics in full doses should be given at once. Sulfonamides are usually effectual, penicillin rarely necessary. The general nursing care as previously outlined is essential. Local instillations containing glycerin and phenol are not necessary and without rational excuse. They are supposed to reduce the congestion in the middle ear and to relieve pain. The latter purpose is better and more promptly accomplished with analgesics. The pain of acute otitis lasts only a few hours, diminishing as soon as the nerves in the drum are no longer being stretched by increasing exudate. I have seen no more prompt relief from the glycerin and phenol preparations. If there is any wax in the ear, they make a mixture which is removed with difficulty. I have seen the drum turned gray by phenol by the formation of a superficial slough, but when this was wiped off, the drum was fiery red. Myringotomy is not needed as often as before the antibiotics came into use, but it cannot be entirely discarded. If the otitis does not resolve promptly, if the drum remains bulging and the temperature high, or if the drum perforates and the discharge remains profuse after three or more days, a myringotomy may be necessary to give drainage.

The abortive treatment of common colds by codeine, or codeine and paraverine, as proposed by Diehl, is often successful in adults. It must be used early, as soon as the feeling of irritation in the throat, slight nasal congestion, and general malaise make the patient realize that a cold is coming on. Unfortunately, the child does not often help the physician with this subjective information, certainly not until he is well along in childhood. Some intelligent and alert mothers are able to interpret the behavior of the child—slight droopiness, anorexia, change in the voice from nasal congestion—and can predict a cold's imminence. The parents of a few of my patients have been successful in aborting colds with codeine and papaverine. When the nose is running freely, it is too late.

The sulfonamides have changed the whole picture of acute respiratory disease in the last few years. They are useful only against secondary bacteria invaders and do not affect in the least the virus which usually initiates the infection. The full consideration of this group of drugs has no place in this discussion. Their greatest value is, of course, in pneumonia due to the pneumococcus or even to the staphylococcus, but the course of atypical pneumonia or virus pneumonia is unaltered. I have seen several patients poisoned by pushing sulfonamides unduly, just because there were persistent signs of consolidation in the lung. Failure to respond to sulfonamides is almost a diagnostic criterion for virus pneumonia. Otitis media, suppurative sinusitis, and cervical adenitis usually respond to sulfonamides. The difference in the course and duration of otitis especially is so remarkable that one must have lived through the two periods, before and after sulfonamide therapy, to appreciate it. Mastoiditis is almost an extinct disease.

The sulfonamides are two-edged swords, however, and the patient can easily be poisoned unless proper precautions are taken. With careful written instructions as to the exact dose and hour of each dose, and as to the necessity of giving

enough water and an alkali, the danger is minimal. The time has passed when every patient given sulfonamides must have a daily urinalysis and blood count. No community has adequate hospital or laboratory facilities to handle patients on that basis. We now know that toxic symptoms do not occur, or are extremely rare, if we use care in dosage and give enough fluid and bicarbonate. Orange juice is the easiest source of bicarbonate, and if a child receives the juice of three or more oranges a day we need not fear a too-acid urine. Bicarbonate as such is unpalatable, hard to administer, and produces gas in the stomach if acid gastric juice is present. Orange juice is palatable, well taken by most children, yields some calories in its sugar, contains ascorbic acid, which does no harm and may be valuable in infection, and helps increase the fluid intake when diluted with water. Citrate or acetate mixtures may be used if there is an orange idiosyncrasy, and even bicarbonate dissolved in iced water may be used for older children. Of the several available sulfonamides, sulfadiazine and sulfamerazine have fewer disadvantages than the rest of the group. They are rarely vomited, maintain an adequate blood level, and are not expensive. The dosage in most infections need not be high, not over one grain per pound in the first day and less than that thereafter. I rarely use sulfonamides for more than three or four days except in severe infections. If they have not done their work in that time they are unlikely to do so. I have made a practice of changing from one to another sulfonamide in patients for whom it is necessary to continue treatment more than four days or when a second infection or relapse indicates a new course of sulfonamides.

Tonsillitis with follicular membrane is one acute pyrogenic infection which does not always yield to sulfonamides in the doses usually given. Many patients will go on to the full four-day course with no apparent effect from the drug. This may be due to greater resistance of the staphylococcus, which is the organism usually present.

The status of sulfonamides as preventives is still questionable. In every acute respiratory infection the physician must ask himself, first, whether the symptoms are due to a virus infection or to bacterial invasion, and second, whether it is justifiable to administer sulfonamides in a case of probable virus infection to prevent secondary bacterial mischief. In an epidemic of colds, many or most of which are followed by otitis media, it certainly seems proper to give sulfonamides for a few days. But in a simple sporadic coryza it is still doubtful whether it is one's duty to give the drug. This question needs further statistical study on a large scale before we shall know the final answer.

Penicillin is in the limelight today and has proved its value in many serious infections, some of which do not yield to sulfonamides. Its uses and indications have been so thoroughly described that space need not be taken here. It is worth noting that penicillin has disadvantages. In the first place, it is still expensive compared with sulfonamides. Oral administration is not entirely reliable. Its parenteral administration is much more trouble, the frequent injections are time-consuming for the doctor or a trained nurse, and they are also painful to the patient. In the home, the single large dose in oil and wax is the best means of administration which we have at present. The aqueous solution, which must

be given every few hours means that the patient must be in a hospital, or have twenty-four hour trained nursing care. Much could be said about the disadvantages of hospitals for the child, of the psychic shock of removal from home, of the neglect which he regularly gets due to shortage and inexperience of nurses, of the difficulty of getting the orders of the doctor carried out, of the shortage of beds, and of many other undesirable aspects. Except for a few serious illnesses in which some special technique is required, most sick children are better off in a good home than in the best hospital. I must protest against the prevalent practice of sending children to hospitals and ordering penicillin for simple, self-limited diseases like tonsillitis, pharyngitis with fever, otitis, or even pneumonia. The cost of even a brief hospital stay, with laboratory work and penicillin, is an unfair burden to many families. Most of these acute diseases can be cured rapidly and efficiently at home with a carefully ordered nursing regime, and about twenty cents worth of sulfadiazine.

Summary

The successful treatment of respiratory diseases depends more on the general care and nursing of the patient than on specific remedies. A careful schedule must be planned with written instructions as to the exact hours for taking temperatures, feeding, giving medicines, and treatments. Symptoms such as nasal obstruction, cough, croup, pain, and restlessness may need treatment. Antibiotics are useful in the treatment of bacterial complications and perhaps in their prevention.

The following is an example of a useful printed form for routine use in treating acute illness:

CARE OF SICK CHILD

REST in Bed, Couch, Big Chair, Carriage. Child may sit up against pillows, **need not lie flat.**
Bed table or lap board with small toys will keep child amused.
Keep warm with light robe or sweater over night clothes while sitting up.
Bedding must not be too heavy, one or two light blankets only.

AIR Keep fresh by opening window often, avoiding direct drafts. Room should be 68°-70°, not warmer.

BATHE each day, sponge or tub.

EVERY 3 **HOURS**

1. **TAKE TEMPERATURE** (rectal) and **write it down.**
2. **FEED** one or more of the following.....
3. **MEDICINES,** *always after food. Crush all tablets with sugar and water.*
   If 102° F. - Aspirin ½ tab. If 104° - bath., 5-7 min.
   Jelly in nose
   Sulfa tablets -(1) Mon at 10 · 4 · 10
   Tues " 7 · 12 · 7
   Wed " 7 · 12 · 7
   Cough Med. 1 tsp.
   If in pain and restless -give ½ "pain tablet" and 3 small tablets

Hours	
7	Cereal, with little milk Toast
10	Orangeade
1	Soup, crackers Ice Cream or Junket
4	Orangeade
7	Cereal or Milk Toast Cooked Fruit or Jello
10	Orangeade

BOWELS must be kept open each morning. Milk of Mag. 2 tsp.
Laxative each night while ill.
Enema each morning, if no movement by 10 AM o'clock.
Use soapy water and give enough to obtain a good movement.

WATER between feedings
As Child improves add
Milk
egg, wheat, Veg.

Fig. 1.

THE PREVENTION OF RESPIRATORY INFECTIONS

In order to prevent respiratory diseases we must have a clear conception of their etiology. The causes of these infections are numerous and complex. They may be divided into groups for clearer understanding.

General Causes.—Crowding in cities, in buildings, in schools, in vehicles, trains, and so forth, obviously increases contact and the opportunities for transfer of infecting agents. Civilization may thus be blamed as the underlying cause of most respiratory disease. The fact needs no repetition that explorers and men in lumber camps and other isolated situations do not have colds until they return to civilized places. Smoke, dust, and pungent fumes add to respiratory tract irritation. Climate in general affects the number of colds in a population, but changeable weather is worse than steady cold, and warm climates are not entirely free from respiratory disease.

Individual predisposition depends to some extent upon abnormalities of the respiratory tract, such as nasal obstruction from septal deviation, adenoids, or greatly enlarged tonsils. Allergy plays a part in the matter, for it not only causes hay fever and asthma, but predisposes some children to respiratory infections as well. This relation is complex, and we have not yet fully solved it. Individual predisposition to a particular kind of cold is frequently seen. Some children always have laryngitis or croup, others have sinusitis or otitis, others bronchitis or asthma, and each is likely to stick to his favorite type of disease.

Precipitating Causes.—These are not always given the consideration they deserve. In every acute infection there must be a set of circumstances which makes the child become ill.

Direct contact with an acute infection or possibly with a carrier of an infecting agent is responsible for many colds. A parent, a servant, or even a casual visitor often brings in a cold, which then spreads around the family unless superhuman vigilance is taken to isolate the first victim. Not all colds, however, can be traced to this source. Many children become ill without discoverable contact. Factors which lower the resistance of the individual are as important as the infectious contact, for with lowered resistance the organisms which are ever present in the nose and throat easily become active. These factors must be appreciated, for it is by attention to them that we may hope to make colds less frequent. They may seem to be only remotely or occasionally responsible for acute or recurrent colds, but careful histories will bring out a very close connection between colds and certain antecedent circumstances.

Digestive disturbances certainly predispose to colds. Indigestion may come from overeating, or from eating indigestible or improper food, or from habitual irregularity of diet, or from eating trash of all sorts. The slight but persistent disturbance due to taking milk or other hearty foods between meals is one of the most common causes of recurrent colds in many children. Stopping the milk, which has been forced upon children in school at mid-morning recess, often diminishes the frequency of colds. This is not a theoretical matter but a fact, based upon careful observation of many children in whom the association is too frequent to be accidental.

Constipation is frequently to blame. The child who skips his daily movement, or who postpones it until late in the day, absorbs toxic substances which surely lower his resistance. If he goes off to school with an empty stomach and a loaded bowel day after day, it is small wonder that he is an easy prey to infections.

Fatigue lowers resistance, and this may be acute fatigue from unaccustomed overexertion or from continuous overactivity, or chronic fatigue from insufficient rest at night or too early omission of naps in the runabout age period.

Chilling is perhaps the most frequent direct cause of colds. We call respiratory infections "colds" because they regularly follow chilling. Cold weather is most dangerous when accompanied by high winds. Adults may not appreciate how much a small child is chilled by cold winds, especially with insufficient out-of-door clothing, even when the temperature is not extremely low. Much could be said about the vagaries of fashion in dressing children, as well as their parents. Bare legs and arms in windy winter weather cannot fail to subtract heat unduly from the child's body. The uneven heating he gets by being bundled up in many layers, except over his legs, is perhaps the worst factor. A girl of 3 years was once brought to my office on a bitter winter day with nine layers of woolen cloth and a fur coat down to her hips and below this a pair of silk socks and thin pumps! Her legs felt like marble, but it had not occurred to her mother that this was an unreasonable costume. Indoor clothing in winter is often insufficient. Even in a house adequately warmed there is always a cold air current on the floor, and it is on the floor that children spend most of their time. Bare legs and arms on the floor easily become chilled. Light overalls and long sleeves give a better protection than the light cotton dresses commonly worn indoors, which are no warmer than those worn in the summer heat. Chilling at night is common in infants and young children. The infant who is put to bed with loosely applied blankets soon kicks them off and becomes chilled. The nursing profession has never solved this matter, and babies in hospitals are terribly neglected in this respect. A baby in the split-back nightgown and a wet diaper, with no blankets over him, is a common sight in pediatric wards. The uncovered infant and runabout is inviting respiratory infection, for the body needs more even covering and temperature in sleep than in waking hours. Clothing manufacturers have met the problem by offering the "sleeper"—a heavy flannel pajama with feet, advertised "to keep the baby warm when he crawls out." Mothers usually leave on the shirt (often double breasted) under the sleeper. The result is that the child is soon too hot and does crawl out, if he is able, but even the sleeper and shirt do not keep him as warm as would a blanket or two. One keeps warm in bed with bedding, not with heavy night clothes. We have met this problem satisfactorily by using a simple bag made of a folded light blanket for infants, and for older children a nightgown with a tape or band at the tail which is tied to the foot of the crib or to the bedspring. With blankets properly fastened to the crib rods, the child stays covered all night. His mother does not have to get up repeatedly to see that he is covered. If her rest is disturbed, she may take a cold which she then transmits to the child! Uncovering is a serious matter, and until the problem is met in every case we must expect defeat in our effort to prevent a child from having recurrent or persistent colds.

Overheated houses are responsible for many respiratory infections. The hot air dries out the mucous membranes, and the heat makes the child perspire.

Any moving current of air may then chill him. In the houses of the well-to-do, where thermostats regulate heat accurately, this is less a factor than in homes heated with stoves, pipeless furnaces, or unregulated steam. Apartment dwellers, who are afraid they will not get their money's worth of heat and who leave their radiators turned on all day, are among the worst offenders. Mothers who wear a thin cotton dress and little else, with bare arms and legs, too often keep the house at a temperature suitable for their costumes, but not healthy for their children. Overheating and subsequent chilling in summer may also precipitate illness. Long exposure on sea-beaches, staying too long in the water, hose parties in the back yard, may be followed by acute colds or tonsillitis. The latter occurs more often in summer than coryza or bronchitis; indeed, tonsillitis is the most common acute illness seen in summer.

Any one of the factors just discussed may cause a child to acquire a cold, but it may take more than one of them. It is a common experience to elicit the following history from a mother whose child has an acute febrile respiratory disease: The child on a holiday skipped his usual morning movement, went on an expedition on which he became overtired, had no midday rest, perhaps was chilled in the water, ate unusual foods at irregular intervals, returned late in the evening, and slept restlessly. Next day he pays the penalty for the debauch by being acutely ill. Whether he has nasopharyngitis, tonsillitis, laryngitis, or bronchitis depends mostly on his own inherent tendency to a particular localization. Direct contact with another infection is not necessary in such cases, yet this child may transmit his activated infectious agent to his siblings.

Vitamins, cod liver oil, and tonics may help build up a child's physical resistance but will not prevent colds if he leads an unhygienic life. Bacterial vaccines by mouth or by injection cannot prevent the virus infections, and it is doubtful whether they build up immunities to secondary invaders. Some patients insist on having cold injections and claim that they have fewer or less severe colds when they receive them. The effect is probably psychic, or they may take better care of their own health in order to be sure the injections do some good. There is no reliable evidence that such injections are justifiable.

In attacking the problem of recurrent or persistent colds, the first step is a careful study of the child's environment, of his diet, and his daily regime. We may be unable to change his home, but we can inspect it and determine whether it is under- or overheated. The child's bedroom, the situation of his bed in relation to windows and doors, the bedding, and night clothes must be studied, and the mother must be taught how to keep him covered and out of direct drafts. His indoor and outdoor clothing must be adequate. The daily regime must be studied from the hour of rising to bedtime and must be carefully arranged. A morning movement must be insisted upon, and this means an early breakfast, one hour before leaving for school, so that there is time for a bowel movement. The diet must be prescribed in writing, and special stress should be laid on the disadvantage of milk between meals. Rest for preschool children after lunch, and for school children on week ends and holidays, helps avert fatigue. The Sunday fatigue from overexertion often precipitates the Monday cold. Careful

physical examination must be made for defects, especially malnutrition, anemia, and nasal obstruction. If remediable, these must be corrected.

With a complete study of all factors we can make colds less frequent, and with earlier treatment usually make them less severe. The child's surroundings can be controlled to a certain extent, depending upon the locality in which he lives, his home and economic status, but most of all on the intelligence and cooperation of his parents. When parents are not bright enough, or too lazy, to follow advice or instructions, the child is bound to be ill from time to time. Some factors cannot be eliminated, especially contact with cases of virulent infections. So children will continue to have a cold or two each winter under the best of care, just as do their parents and their physicians!

Clinical Conference

CONFERENCES OF THE CHILDREN'S HOSPITAL WASHINGTON, D. C.

1. Conference on Infantile Cortical Hyperostoses (Caffey-Smyth Syndrome)

DR. FREDERIC G. BURKE.—R. G., a 3½-month-old white male infant, was first admitted to Children's Hospital on May 25, 1946, with the chief complaint of fever and irritability. The illness had begun one week previously with a swelling about the right side of the face. This was associated with irritability, which, together with the fever, continued on up to the hospital entry. The day before admission the temperature rose to 105° F., at which time the child seemed to have some twitchings of the arms and legs, but there were no frank convulsions. The past history revealed the child had had some difficulty with his formula at the age of 4 weeks and also had had some mucus and blood streaks in his stools. The formula was adjusted several times, and the stools became normal. The baby gained weight in a normal fashion. Vitamin supplements had been administered in adequate amounts since the age of 4 weeks.

The family history revealed that the patient's paternal aunt had had active tuberculosis six years previously and that she had been in a sanatorium where a pneumothorax and phrenicectomy were done. Allegedly, her infection had been inactive for the past four years. She took care of the baby for four to five days during the second week post-partum and wore a mask during this time. She had also visited the baby intermittently since then. The child's mother had always had negative chest x-rays and sputum until two or three weeks previously when a chest x-ray was thought to show some calcification in the right lung. The mother had had several episodes of pleurisy since the age of 16. A sputum examination done on the mother shortly before the infant's admission was negative for tubercle bacilli.

Physical examination at the time of admission revealed a well-developed, well-nourished 3½-month-old infant who appeared acutely but not critically ill. The temperature was 104.4° F. There was a swelling on the right side of the face which extended superiorly to the upper level of the ear and down to the angle of the jaw. This area was tender and indurated but nonfluctuant. There was no inflammation of Stensen's duct and no palpable calculi. The liver and spleen were palpable one fingerbreadth below the costal margin. The heart and lungs were negative, and the remainder of the physical examination was essentially normal.

Cases presented from the Medical and Surgical Services, Dr. Joseph S. Wall, Chief of Staff.

Laboratory examination showed a hemoglobin of 8.5 Gm. with 3.2 million red cells; the white cell count was 14,100 with 66 per cent polymorphonuclear cells, 29 per cent lymphocytes, 3 per cent monocytes, and 2 per cent eosinophiles. Platelet count was 150,000. Subsequent repeat hemograms showed a consistent leucocytosis ranging between 13,000 and 16,000 with an essentially normal differential. Urinalysis was negative. Examination of the spinal fluid was negative as were the febrile agglutinins. An x-ray of the chest revealed a pericardial shadow in the third to fifth interspace on the left, the nature of which was not known. Roentgen examination of the bones of the face revealed no evidence of periostitis at this time. Complement fixation test for mumps performed at the National Institute of Health was reported as negative. A tuberculin test (O.T. 1:1,000) was done, and within twenty-four hours an area of erythema measuring 2 cm. in diameter was observed. However, this erythema subsided so that at the end of forty-eight hours it was only minimally present. A repeat tuberculin test (O.T. 1:100) was negative, and P.P.D. No. 2 similarly showed no positive reaction. Gastric washings for tuberculosis organisms were performed at this time, and of five consecutive examinations, four were positive for tubercle bacilli on smear, while culture of the washings on Petragnani's media grew out tubercle bacilli on three occasions. A provisional diagnosis of primary tuberculosis was made on the strength of these positive gastric washings.

During the course in the hospital the child's temperature fell gradually during the first week and then remained low grade. The swelling upon the right side of the face subsided somewhat but did not completely disappear, and it remained quite tender. The baby took his formula moderately well and gained weight. Therapy during this admission consisted of penicillin (20,000 units every three hours for seven days) and then sulfadiazine for four days. However, neither drug appeared to exert any favorable influence on the course of the disease. He was discharged after a twelve-day hospital stay to be followed in the dispensary.

At home the child continued to have a low-grade fever and was moderately irritable. The swelling of the right side of the face remained and occasionally became more marked. About two weeks after discharge it was noted that the left side of the face was becoming similarly involved. One week later a painful tender swelling was noted along the left forearm. An x-ray of the long bones taken at this time showed a periostitis along the shaft of the left ulna at the distal end, and it was thought that this lesion represented a tuberculous periostitis. The child was then readmitted to the hospital for treatment with streptomycin.

Physical examination at this time revealed a fretful 4-month-old infant who appeared chronically ill. Both sides of the face showed a marked, brawny, tender edema extending from the lower lobe of the ear to the angle of the jaw (Fig. 1). Stensen's duct did not seem to be involved. There was a diffuse swelling and marked tenderness along the distal end of the left arm. Heart and lungs were negative. The liver and spleen were palpable one fingerbreadth below the costal margins. The rest of the examination was essentially negative. The temperature was 102.6° F.

Laboratory examination revealed a hemoglobin of 10 Gm. with 3.5 million red cells; the white count was 27,000 with 53 per cent polymorphonuclear cells, 46 per cent lymphocytes, and 1 per cent eosinophiles. Repeat urinalyses were negative. The blood culture taken shortly after entry was sterile. Sedimentation rate was normal. A gastric washing performed prior to the initiation of streptomycin therapy revealed a rare acid-fast bacillus on smear. X-ray examination of the long bones of the upper and lower extremities revealed some periosteal thickening of the bones of the upper extremities with some increase in the width of the distal portion of the ulna (Fig. 2). X-ray examination of the chest revealed no essential change since the previous film taken on May 29.

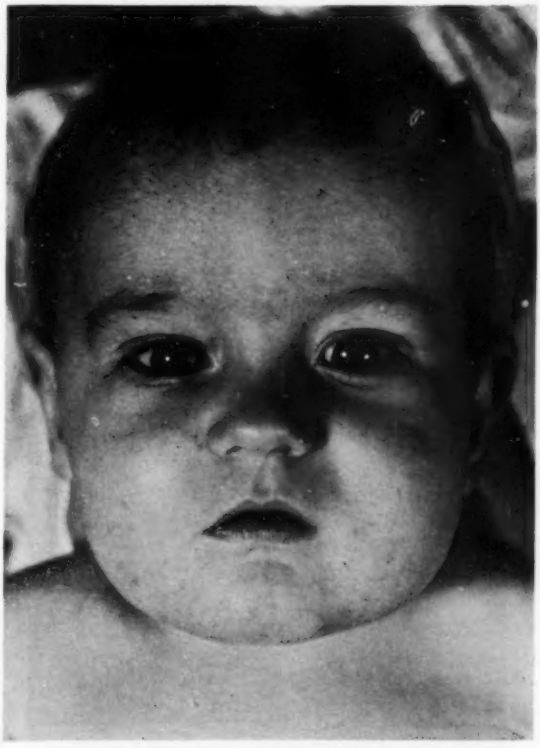

Fig. 1.—R. G. at the time of readmission to the hospital. Note the marked bilateral facial edema.

Roentgenologic examination of the skull in the anteroposterior and lateral positions revealed no definite evidence of abnormality. Wassermann and Kahn tests were negative. Serum calcium was 11.5 mg. per cent and phosphorus was 3.3 mg. per cent. The ascorbic acid level was 0.369 mg. per cent. A blood sample was sent to the National Institute of Health for complement fixation virus studies and was found to be negative.

On June 27, the day before the second admission, the patient was started on streptomycin with a dose of 30,000 units every three hours intramuscularly. For the first two weeks in the hospital the temperature remained elevated in the neighborhood of 101° to 102° F.; subsequently it came down to normal by lysis, and the child remained afebrile during the remainder of his hospital course. The patient slowly gained weight, and his appetite remained moderately good. The bilateral facial swelling gradually diminished and had completely disappeared within two and one-half weeks. Swelling and tenderness of the ulna also subsided progressively and disappeared in approximately the same interval of time. The sedimentation rate, which had been normal at the time of entry, rose to 39 mm. per hour (Winthrobe) within two weeks and remained substantially elevated (ranging between 22 and 45 mm. per hour) during the next month in the hospital. Repeated white counts showed a leucocytosis varying between 9,000 and 22,000 with the neutrophiles ranging from 17 to 60 per cent.

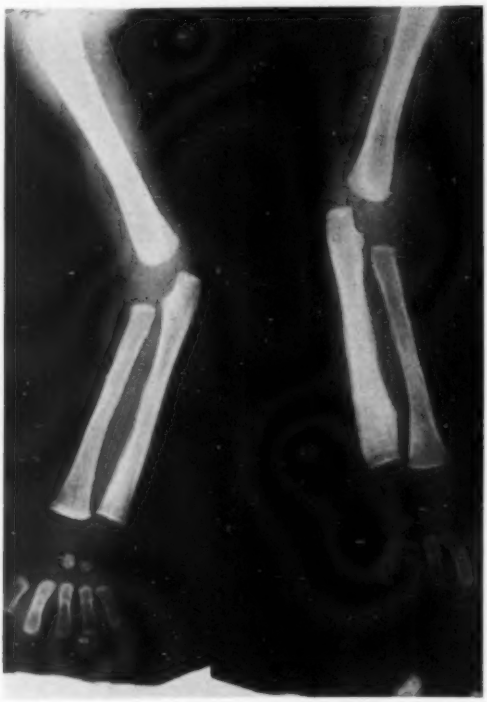

Fig. 2.—R. G. X-ray of the extremities reveals a periosteal lamellated thickening of the long bones.

While on streptomycin therapy, repeat gastric washings were obtained for tubercle bacilli, and with the exception of one washing on July 11 which yielded a rare acid-fast bacillus on smear, all the other specimens, eleven in number, were negative both on smear and culture.

Within three weeks after admission, repeat x-ray examinations of the left ulna revealed evidence of healing of the periostitis noted at the time of admission. On August 12, x-ray examination of the thorax revealed some periostitis of the left clavicle and of the fifth rib anteriorly and the eighth rib posteriorly, similar in effect to the lesion involving the left ulna. A re-examination of the mandible on August 22 revealed a rather diffuse periostitis bilaterally on the inferior surface of the mandible. X-ray of the left ulna taken on August 28 just before discharge showed continued resorption of the previously described periosteal proliferation. On August 11 an exacerbation of the edema of the face was noted bilaterally and was quite tender and swollen. There was no concomitant temperature elevation, and the facial swelling subsided gradually during the course of the next three weeks with only slight residual nontender swelling remaining on the left side. Streptomycin was discontinued on August 17 after forty-seven days of therapy; the amount of drug administered totaled approximately 12 million units. No untoward effect from streptomycin was noted during the interval of its administration.

On August 22, one week prior to discharge, the sedimentation rate had returned to normal and the patient appeared clinically well. The infant was discharged on August 29, after a two-month stay in the hospital.

Follow-up x-ray examinations during the next six months showed continued and progressive healing of the previously noted areas of periostitis of the left ulna, clavicle, ribs, and mandible. The facial edema has completely disappeared, the temperature has remained within normal limits, and the infant appears completely well.

DISCUSSION

DR. SIDNEY ROSS.—This patient represented a diagnostic problem for a considerable period of time and probably would have remained so had it not been for the fortuitous simultaneous publication of a paper by Smyth, Potter, and Silverman,[1] in which were reported seven cases of a new syndrome which bore a striking similarity to our case. In common with our patient, the patients of Smyth and his associates showed marked irritability, fever, anemia, periosteal involvement, and a characteristic brawny, tender facial edema. There was little doubt following this report that our case fitted into this syndrome. Since attention has been called to the entity, nine additional cases of this syndrome have been diagnosed during the past eighteen months at Children's Hospital; two of the cases have been culled from our hospital records by reviewing all charts of infants under 6 months who had a discharge diagnosis of scurvy; a re-examination of their x-rays together with a review of the protocol indicated rather unequivocally that both cases were examples of this new disease entity. A detailed account of these cases will be discussed in a forthcoming report.[4]

In 1945 Caffey and Silverman[2] first described four cases of this syndrome, which they termed infantile cortical hyperostoses, presenting the symptoms previously noted. The basic roentgen change as described by Caffey was an external thickening of the corticalis, which was lamellated in many instances. Bones involved included the mandible, clavicle, scapula, ribs, and extremities. The soft-tissue swellings preceded the formation of the hyperostoses in the neigh-

TABLE I. A COMPILATION OF THE FINDINGS IN THE THIRTEEN INFANTS UNDER 7 MONTHS OF AGE REPORTED BY CAFFEY AND SMYTH

CASE NO. AND SEX		AGE OF ONSET	FEEDING HISTORY	FEVER	IRRITABILITY	BRAWNY EDEMA OF FACE	W.B.C.	TUBERCULIN TEST	VIT. C LEVEL (MG. %)	SEROLOGY	SEDIMEN. RATE	OUTCOME
1	F	5 mo.	Adequate	+	+	+	16,000-24,000	Neg.	0.12	Neg.	Elev.	Recov.
2	F	5 mo.	Adequate	+	+	+	12,000	Neg.	0.10	Neg.	Elev.	Recov.
3	M	7 mo.	Adequate	+	+	+	14,000-20,000	Neg.	0.085	Neg.	Elev.	Recov.
4	F	3 mo.	Adequate	+	+	+	23,000	Neg.	.44	Neg.	Elev.	Recov.
5	F	4½ mo.	Adequate	+	+	+	23,000-37,000		1.35			Recov.
6	M	2 mo.	Adequate	+	+	No	13,000	Neg.	Low blood, high urine	Neg.	Elev.	Recov.
7	M	2 mo.	Adequate	+	+	+	6,000			Neg.	Nor.	Recov.
8	M	2½ mo.	Adequate	+	+	+	14,000	Neg.		Neg.		Recov.
9	M	3 wk.	Adequate	No	No	+		Neg.		Neg.		Recov.
10	F	4 mo.	Adequate	+	+	+	13,000	Neg.		Neg.	Elev.	Recov.
11	M	2 mo.	Adequate	No	No	+	11,000-21,000					Recov.
12	F	4 mo.	Adequate	+	+	+				Neg.		Recov.
13	M	3 mo.	Adequate	+		+	7,000-29,000	Neg.		Neg.		Recov.

TABLE II. A COMPILATION OF THE SITE OF PERIOSTEAL INVOLVEMENT IN THE THIRTEEN PATIENTS UNDER 7 MONTHS OF AGE REPORTED BY CAFFEY AND SMYTH

CASE NO.	MANDIBLE	CLAVICLE	SCAPULA	RIBS	EXTREMITIES
1	+	0	0	+	0
2	+	+	0	0	+
3	+	+	0	0	+
4	+	0	0	+	0
5	0	0	0	0	0
6	+	+	0	+	+
7	+	0	0	+	+
8	+	+	+	+	+
9	+	+	+	0	+
10	+	+	0	0	+
11	+	0	0	0	0
12	+	0	0	0	+
13	+	+	0	0	0
	12	7	2	5	8

boring bones and have occurred in the face, thorax, and extremities. The active manifestations in Caffey and Silverman's patients subsided completely after several weeks with no serious complications.

In spite of the general objections to eponyms in medical nomenclature, we have referred to the syndrome as Caffey-Smyth disease in our cases at Children's Hospital in view of the obscure etiology of the syndrome. In addition, it has been our impression roentgenologically that the skeletal lesion was primarily a periosteal reaction rather than a cortical involvement.

Thus far there has been a total of seventeen cases of this syndrome reported in the literature.[1-3] Of these, thirteen were in infants under 7 months of age. The ten cases of Caffey-Smyth syndrome diagnosed at Children's Hospital during the past eighteen months have similarly all been in children under 7 months of age.

A compilation of the findings in the thirteen infants under 7 months of age reported by Caffey and Smyth is set down in Table I. As will be noted, the feeding history including vitamin supplements was adequate in every case. Fever and irritability as well as the characteristic brawny, tender, nonhyperemic facial edema were noted in all patients but one. The white cell count was increased in the majority of instances, and there was usually a lymphocytic predominance. The tuberculin test as previously noted was negative in every patient where it was performed in the series reported by Caffey[2, 3] and Smyth.[1] (In the case reported here the tuberculin was equivocally positive, but all our other nine patients had negative tuberculin tests.) Vitamin C levels were not singularly aberrant. Similarly the serology was negative in all patients. In the majority of instances where it was performed, the sedimentation rate was elevated. The periosteal skeletal involvement was widespread, as will be noted in Table II. The mandible was involved in every patient but one and accounted for the frequency of the brawny edema of the overlying soft tissue of the face; the latter was by far the most striking presenting symptom and permitted a provisional diagnosis to be made on sight in the majority of cases. The clavicle and extremities were other frequent sites of periosteal involvement. In one case seen at Children's Hospital, the only bony involvement was noted in the left scapula.

The etiology of this new syndrome remains obscure. Scurvy has been considered in the differential diagnosis in view of the periosteal bone involvement. However, the usually noted scorbutic bone changes, such as the zone of rarefaction beneath the epiphyseal line, the ground-glass appearance of the shaft, the Wimberger rings, and the absence of any subperiosteal hemorrhage on biopsy, would militate against a diagnosis of scurvy. In addition, the age of the onset of the syndrome (i.e., mostly 3 to 4 months) as well as the history of adequate vitamin C intake and lack of response to vitamin C would similarly be against a diagnosis of scurvy.

As for an infectious etiology, which is suggested by the increased white blood count, fever, and elevated sedimentation rate, there is not too much definitive evidence. Blood cultures and febrile agglutinations were negative in all cases, and there was no perceptible response to sulfonamides or penicillin. Biopsy specimens have similarly not been in keeping with a diagnosis of an infectious process. Smyth[1] and Caffey[2, 3] mention that virus studies were not done in their cases. However, complete virus studies were performed at the National Institute of Health in five out of our ten cases, and all were negative. Syphilis can be ruled out on the basis of negative serologies, both in the patients seen at Children's Hospital as well as those reported by Caffey[2, 3] and Smyth.[1] As for tuberculosis, we were initially under the impression that we were dealing with an acid-fast infection in the case reported here, in view of the positive gastric washings and history of exposure to tuberculosis. However, the generalized periosteal involvement was unlike the bony lesions described in tuberculosis, and, more important, the subsequent nine patients have had negative tuberculin tests and repeated negative gastric washings. Similarly in the seventeen cases described by Caffey and Smyth, tuberculosis was rather effectively ruled out. We can only conclude that the tuberculous infection in the present patient was coexistent and coincidental and was unrelated to the syndrome.

The possibility that the lesion may be of a sarcomatous nature as suggested by the laminated periosteal reaction is ruled out by the benign course of the disease together with the absence of any evidence of sarcoma on biopsy. Similarly, traumatic ossifying periostitis seems to be excluded. The disease at its onset may similarly be confused with parotitis as well as osteomyelitis of the mandible and neoplasm of the mandible.

In every case reported thus far as well as in our own ten cases, the disease was benign and ran a self-limited albeit a protracted course, sometimes lasting for months. The excessive irritability, slow weight gain, and poor feeding habits of the infant make this disease a sore trial for the parents. However, a good prognosis can be categorically given in every case once the diagnosis is made.

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2. Conference on Pericarditis With Effusion

DR. ELMER FANTAZIER.—M. M., a 5-year-old white girl, was admitted to this hospital on Jan. 19, 1948, with the chief complaint of fever and pallor.

The present illness began five days prior to admission when she complained of nausea and felt unusually warm. She vomited following breakfast and was unable to retain food for forty-eight hours. There was no diarrhea. The symptoms slowly subsided during the ensuing forty-eight hours, and the patient was allowed limited activity. On the morning before admission it was noted that the child was listless and had developed considerable pallor. On the day of admission she complained of pain in her left chest on movement, and the pallor was increased.

The past history revealed that the patient was the product of a nine months' gestation and an uneventful delivery. Her birth weight was 7 pounds. The neonatal period was not remarkable. Measles occurred at 4 years, from which she made a slow but uneventful recovery. The mother stated that the patient had had "flu" last winter, from which the convalescent period was about three weeks.

The family history revealed that there were two siblings, both living and well. There was no history of familial or constitutional diseases.

Physical examination showed a poorly nourished white girl who appeared acutely ill. The temperature was 100° F., and the pulse was rapid and thready. The blood pressure was 88 systolic, 58 diastolic. The skin was very pale and moist; no petechiae or rashes were noted. Palpable cervical nodes were present. The pharynx was moderately injected, and a thick white exudate was noted on the right posterior pharynx. There was a questionable friction rub over the lower left lung field anteriorly. The heart was enlarged to the left on percussion, and the sounds were muffled, distant, and rapid. No murmurs were heard. The liver was palpable three fingerbreadths below the costal margin. The spleen was not felt. A fecal mass was palpated in the left lower quadrant of the abdomen. No abnormalities of the extremities were noted, and the reflexes were physiologic.

An x-ray taken shortly after admission showed the heart to be enlarged to the right and left (Fig. 1). The cardiac contour was "water bottle" in type, indicative of dilatation and some pericardial effusion.

A blood count on admission showed a hemoglobin of 12 Gm. with 3.9 million red blood cells; the white count was 16,900 with 85 per cent polymorphonuclears, 8 per cent lymphocytes, and 7 per cent monocytes. Urinalysis was negative, as was the tuberculin patch test.

On the day of admission the patient was seen in consultation by Dr. Bernard J. Walsh.

The patient was given sulfadiazine initially in a dose of 7.7 gr. every four hours, and Digifolin, 1½ gr. three times a day, but she began to vomit the medications after the third dose of sulfadiazine. She was then given an infusion of 200 c.c. of 5 per cent glucose in saline slowly over a period of an hour, and penicillin was substituted for the sulfadiazine.

The child was fluoroscoped twice within twenty-four hours after admission. Following the second fluoroscopy, a pericardial tap was done by Dr. Walsh, and 200 c.c. of fluid were obtained; the first 20 c.c. were clear yellow, while the remainder of the fluid was a medium brown color. Following the pericardial tap there was considerable clinical improvement. Analysis of the pericardial fluid obtained from the tap was as follows:

	Light Fluid	*Dark Fluid*
Cells	5,000	8,000
R.B.C.	13%	8%
W.B.C. Polymorphonuclears	77%	91%
Lymphocytes	6%	1%
Mononuclears	4%	1%

Specific gravity: 1.018
Smear and culture of fluid: Negative.

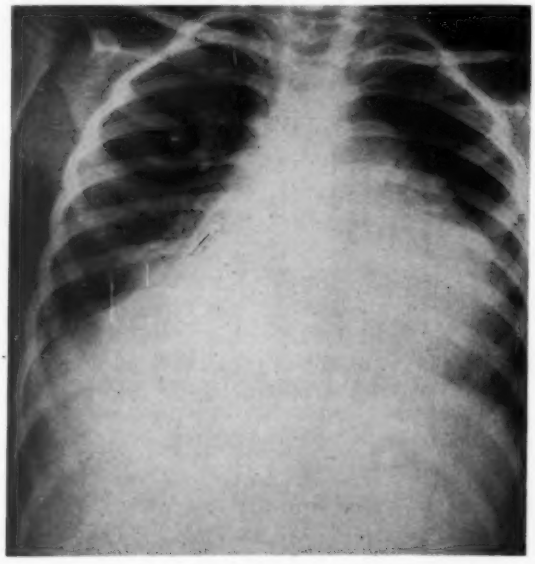

Fig. 1.—M. M. X-ray of the heart taken on admission revealing considerable cardiac enlargement to the right and left. The cardiac contour has a "water bottle" appearance suggestive of pericardial effusion.

The patient has been on penicillin, 50,000 units every three hours intramuscularly, since the onset of vomiting on the second hospital day. She also received a maintenance dose of 8 minims of tincture of digitalis by mouth daily. The child is taking fluids well and eating soft foods now. The temperature has remained at about 100° to 101° F. since the pericardial tap on Jan. 20, 1948.

Clinically the patient has shown steady improvement. The heart continues to be enlarged to the left on percussion, but the heart sounds are more readily heard.

A chest film taken on the day of discharge is shown (Fig. 2). As seen by repeated fluoroscopic examinations, there has been considerable reduction in the cardiac-pericardial size. The pulsations along the cardiac borders gradually increased in amplitude. The liver enlargement slowly receded and became less tender. She was discharged on Feb. 2, 1948.

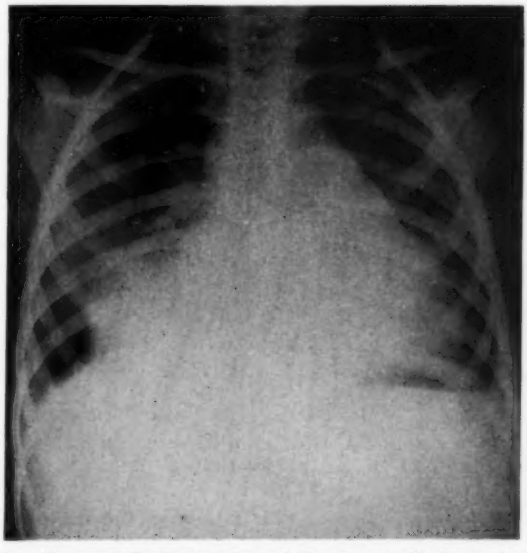

Fig. 2.—M. M. X-ray of the heart taken at the time of discharge showing some reduction in the cardiac-pericardial size. Subsequent fluoroscopy two and one-half weeks later showed the cardiac contour to be normal in size and shape.

DISCUSSION

Dr. Bernard J. Walsh.—When I first saw this patient shortly after her admission to the hospital, I found her lying flat, in no respiratory distress, and with moderate facial pallor. There was no edema or cyanosis of the extremities. The cardiac rhythm was normal. There was no gallop. I was unable to hear any sounds indicative of friction rubs, either pericardial or pleural. No murmurs were heard. The heart sounds were moderately distant. The area of cardiac dulness was considerably increased, extending to about the anterior axillary line in the fourth and fifth left interspaces. There was a flat note on percussion with distant breath sounds over the lower third of the right chest posteriorly. The liver was smooth and slightly tender, and the edge was readily felt three fingerbreadths below the costal margin in the right midclavicular line.

The electrocardiogram (Fig. 3) was within normal range, although there was very slight elevation of the S-T segments in Lead I consistent with acute pericarditis.

Fluoroscopic examination showed a large cardiac-pericardial shadow with very poor to absent pulsations on all borders. The enlargement was chiefly to the left. There was a wedge-shaped density at the cardiohepatic angle on the right, the nature of which was not clear, but it seemed more consistent with fluid in that area than with pneumonic infiltration.

A diagnosis of acute pericarditis with pericardial effusion, cardiac tamponade, and possible myocardial failure was made.

In view of the possibility that some degree of heart failure was present, digitalis was recommended.

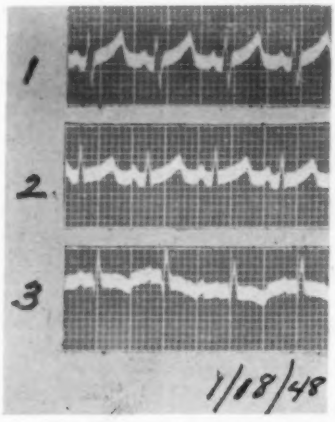

Fig. 3.—Ecg. showing slight elevation of S-T segments and Lead I.

Late on the second hospital day I again saw the patient, and it was apparent that she had grown worse. She was in no particular respiratory distress and was able to lie flat, but she looked much more ill and her facial pallor had increased. The liver had further enlarged. A pericardial tap was done immediately, the needle being inserted in the fifth interspace, approximately 1.5 cm. inside the left border of cardiac dulness. The first 20 c.c. of fluid were light yellow and clear. The remainder of the fluid was dark amber. It was believed that the difference in color resulted from pocketing of the fluid. When about 100 c.c. of fluid had been withdrawn, the patient seemed much improved. When she was returned to her room, it was apparent to all who had seen her before the pericardial tap that she was materially better. Her liver became much less tense and diminished in size by 1.5 to 2 cm.

Pericarditis due to any cause is unusual, both in children and in adults. It is not rare in children, however, this patient being the third we have had in this hospital in the past six months. The cause of the pericarditis, even when there is a good deal of pericardial effusion, remains unknown in the majority of our cases. Pericarditis associated with rheumatic fever makes up approximately 30 per cent of the cases of acute pericarditis we have seen in this hospital. Another 10 per cent of the patients have purulent pericarditis due to the

influenza bacillus, the pneumococcus, or to other organisms. After the diagnosis of pericarditis is made, the next most important decisions concern effusion. If effusion is present, is it causing increasing restriction of the heart? Is it purulent, or not? If there is a leucocyte count of 20,000 or over, and particularly if there is a temperature of 103° F. or more, I believe a purulent pericarditis must be strongly suspected, and it is best to do a pericardial tap. If the effusion is purulent, it is seldom possible to remove the pus except by surgical drainage. If the patient with pericarditis has a large liver and/or orthopnea,

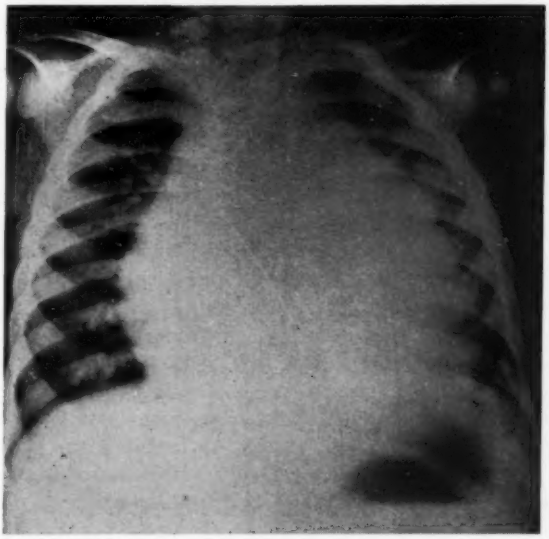

Fig. 4.—J. M., 16-month-old child with acute pericarditis with effusion. X-ray of the heart at the time of admission revealed a considerably enlarged cardiac-pericardial shadow. The cardiac size subsequently returned to normal.

even though high fever and considerable leucocytosis are absent, cardiac tamponade can be considered practically certain. It is our practice to observe such patients carefully for increase in the size of the liver and increase in the size of the cardiac-pericardial shadow. If increase is noted by comparison with the first examination, then a pericardial tap is carried out and as much fluid as possible is removed. However, pericardial tap, either because of possible purulent pericarditis or increasing cardiac tamponade, needs to be done only occasionally. In the vast majority of patients, the infection subsides over a period of six or eight weeks, accompanied by steady decrease in the size of the liver and in the amount of fluid in the pericardium.

The x-rays (Fig. 4) show a large cardiac-pericardial shadow in a 16-month-old child who was on the medical service here recently. The second film was taken when the child was ready to leave the hospital. The etiology remains unknown for this patient also. It was not necessary to tap the pericardial sac.

This is the youngest patient I have ever seen with pericarditis. I have seen her recently in the Cardiac Clinic, and she is now well, leading an active normal life. The cardiac-pericardial shadow has returned to normal. The cardiac pulsations are vigorous in all views by fluoroscopic examination.

Addendum.—Feb. 18, 1948: The patient was examined today. She has been eating well and has no complaint. She has seemed to her parents to be quite her usual self. On examination she appeared in good health. The cardiac rhythm, rate, and sounds were normal. The heart sounds were vigorous and loud. There was no edema or cyanosis. There was no enlargement of the liver. Fluoroscopic examination showed a full-sized, normal appearing heart with very vigorous pulsations except in the region of the right auricle.

3. Conference on Actinomycosis, With Pulmonary Involvement

DR. ROBERT C. GARBY.—L. S., a 9-year-old Negro girl, was admitted to Children's Hospital on Dec. 14, 1947, with the chief complaint of a "knot in her throat." Recently she had been fairly well until about ten days prior to entry when she had a cold accompanied by a nonproductive cough and marked malaise, and stayed in bed. The cough was aggravated, and there was some dyspnea while lying flat on her back. Her neck had been stiff for three days, and the night before admission pain was noticed in the neck.

The past history revealed that her first admission to the hospital was on June 29, 1945, for gonorrheal vaginitis, which was treated with penicillin with good results. She was discharged on July 11, 1945, thirteen days after admission. Her next hospital admission was at Gallinger Hospital of this city on Jan. 14, 1946. The diagnosis of left lobar pneumonia was made. She showed marked toxicity during the first week of her hospital stay. The temperature fell by lysis, being normal on the sixth day, and her chest cleared slowly. X-rays showed considerable pneumonic infiltration on the left side. Clubbing of the fingers and toes was noticed at that time.

The next hospital admission was on Aug. 1, 1946, when she had a "knot on left shoulder," had had a cold and cough for several weeks, and her fingers and toes had been swollen for one week. Physical examination at that time showed a firm, fixed, nontender mass protruding from the left chest anteriorly. There was dulness to percussion lateral to the mass and scattered dulness in the left chest posteriorly. Moist râles were heard throughout the left chest with increased breath sounds and scattered râles in the right lung. The fingers and toes were clubbed.

Laboratory examinations revealed a hemoglobin of 12 Gm., with 4.3 million red blood cells and 11,300 white blood cells with 65 per cent neutrophiles (58 per cent segmented and 7 per cent stab cells), 3 per cent eosinophiles, and 32 per cent lymphocytes. The urine was clear and acid, with a specific gravity of 1.020, albumin 5 mg. per cent, and many white blood cells in clumps.

Repeated blood examinations through August 14 showed a leucocytosis ranging between 11,000 and 17,000 with essentially similar differentials. Repeated urinalyses were essentially negative. No Bence-Jones protein was found. Repeated sputum cultures, concentrated smears, and gastric washings for

tuberculosis were negative. Fluid aspirated from the mass on the chest showed a hemolytic *Staphylococcus aureus* on one culture, and on another examination a fungus was found which the National Institute of Health considered to be a nonpathogen and probably an air contaminant.

Treatment consisted of 20,000 units of penicillin intramuscularly for three days, and again six weeks later 50,000 units of penicillin intramuscularly every three hours were given for forty-eight hours for a return of the gonorrheal vaginitis. The cough gradually cleared over a period of two months, the x-rays cleared somewhat, and she was discharged on Nov. 10, 1946, to be followed as an outpatient.

Her developmental history showed that she did not walk or talk until the age of 2½ years, and her dentition was markedly delayed. Cod liver oil and orange juice intake was believed to have been deficient. For several years she has had epileptoid seizures lasting five to ten minutes during which she "sees" her mother who died of a "nervous breakdown."

Physical examination on the day of her present hospitalization revealed a chronically ill, poorly developed, and poorly nourished child. The temperature was 100.4° F. and respirations 20. There was a tender swelling about the size of a small lime in the suprasternal region, which was fluctuant, moderately fixed, and did not move on swallowing. Congestion of the nasal mucosa was present, and the tonsils were inflamed and hypertrophied. Examination of the lungs revealed increased dulness over the left lower lobe. On deep palpation of the abdomen, slight tenderness in both lower quadrants was present. There was a shallow, indolent-appearing ulcer over the left side of the sternum, surrounded by a dark, leathery discoloration about 3 cm. in diameter. There was marked clubbing of the fingers and toes, as well as cervical, axillary, and inguinal lymphadenopathy.

Laboratory examination of the blood revealed a hemoglobin of 9.5 Gm., 3.9 million red blood cells, 11,500 white blood cells, and 79 per cent neutrophiles (72 per cent segmented and 7 per cent stab cells), 1 per cent eosinophiles, and 20 per cent lymphocytes. Sedimentation rate (corrected) was 34 mm. per hour. On Dec. 20, 1947, the blood sugar (fasting) was 83 mg. per cent; Kahn and Mazzini tests for syphilis were negative; an ECG was interpreted as being within normal limits.

On Dec. 27, 1947, microscopic examination of material obtained from aspiration of the swelling in the neck was found to be typical of actinomycosis. Biopsy of a left axillary gland was done on Dec. 22, 1947, and was reported as chronic hypertrophy; no actinomycosis was seen. One routine blood culture done here was negative. A blood culture for fungi which was done at the National Institute of Health was negative. Total blood protein shortly after admission averaged about 9 mg. per cent, and the albumin-globulin ratio was reversed, averaging 0.6/1. Gastric washings for actinomycosis have been negative thus far.

A chest x-ray on the day after admission (Fig. 1) was interpreted as follows: "Examination of the chest reveals the cardiac contour to be 'water-bottled' in shape with a loss of the cardiophrenic angles and enlargement to the

right and left of the entire silhouette. This has the appearance of pericardiac effusion with cardiac enlargement. The interlobar fissure is thickened on the right and contains a little fluid, and there is some low-grade infiltration in the lower half of the left lung. Chronic granulomatous disease with cardiac involvement should be ruled out." Four days later another report reads: "Fluoroscopic examination of the chest in the upright, prone, and head-down positions reveals a definite increase in the supracardiac shadow in the head-down position. This represents some pericardial fluid though not enough for pericardial tapping. . . ." On Feb. 6, 1948, the x-ray report reads: "Re-examination of the chest by fluoroscopic and radiographic techniques reveals adequate pulsations of fair amplitude of the heart. . . . There is considerable reduction in the size of the cardiac silhouette. There is some reduction in the amount of infiltration, and at the present time there is some fibrosis and calcification at the roots." The last x-ray report on Feb. 10, 1947, "reveals the cardiac silhouette to be even smaller than at the previous examination. . . ."

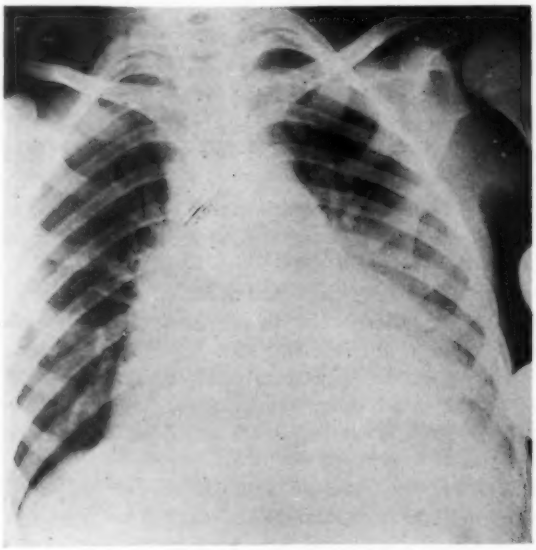

Fig. 1.—Actinomycosis of the lung and pericardium.

Sulfadiazine, one gram every four hours, was begun on Dec. 27, 1947, when the diagnosis was established. After the gastric washings were obtained, penicillin, 100,000 units every three hours, was begun on Jan. 7, 1948. On Jan. 12, 1948, many sulfonamide crystals were found in the urine, and sulfadiazine was discontinued and Citra-Sulfa was substituted. High protein diet, whole blood transfusions, intravenous plasma, and supplementary vitamins have completed the therapeutic measures.

During the first month of the patient's hospital stay the temperature ranged irregularly from normal to 100° or 101° F. daily. Since that time it has decreased to a maximum of about 99.8° F. daily (rectal). Objectively and subjectively there has been marked improvement with considerable increase in strength, brightening of the mental picture, and disappearance of the cough. The suprasternal abscess ruptured on Dec. 18, 1947, drained for about two weeks, and then closed and has remained closed. The chest lesion has apparently healed completely, leaving considerable scar formation.

Follow-up Note, Feb. 29, 1948.—Clinically this child continues to show vast improvement and response to treatment. This is reflected by the chest film (Fig. 3). She still continues to evidence a low-grade fever, however, with a temperature of about 100° F.

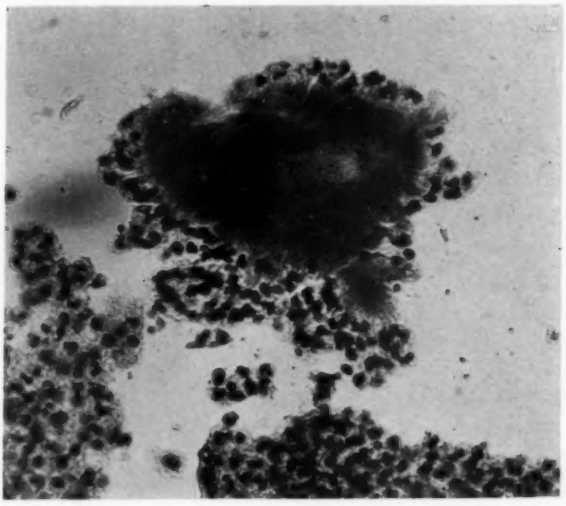

Fig. 2.—L. S. Microscopic section revealing the typical sulphur granules of mycelial growth characteristic of *A. bovis*.

DISCUSSION

DR. THOMAS BRADLEY.—This case illustrates several characteristic features of actinomycotic infections of the lungs and chest wall. First, there is evidence that the lesion is of quite long duration. In June of 1945 the child was admitted to Children's Hospital with gonorrheal vaginitis, at which time it was noted that there were coarse ronchi during inspiration. There was no clubbing of the fingers at that time. She was given oral penicillin in doses of 20,000 units every three hours for ten days. It is not unreasonable to suppose that the fungous infection was present at that time and that it was possibly affected by the treatment. About six months later she was treated in Gallinger Hospital for lobar pneumonia with sulfathiazole, and at that time clubbing of the fingers

was noted. She was discharged from Gallinger Hospital after twenty-three days of treatment with residual changes in the base of the left lung which were thought to be due to pneumonia. She was again admitted to Children's Hospital in August of 1946 with a definite suspicion that actinomycosis was the cause of the persistent lung pathology, but a careful search for the fungus was unsuccessful. Poppe reports that in nineteen cases seen at the Barnes Hospital the diagnosis was not made in several cases until two or three years of intermittent study had been made.

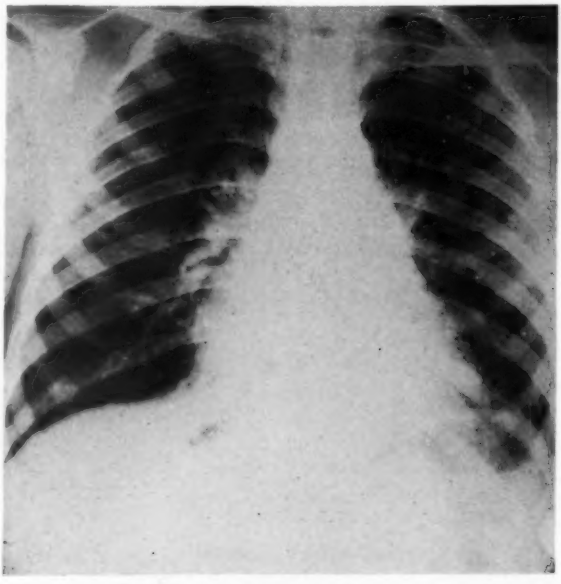

Fig. 3.—Actinomycosis showing marked clearing from the parenchyma and pericardium. There is still considerable fibrosis at the roots.

The advent of chemotherapy has brightened the outlook in actinomycotic infections, but it must be remembered that patients recovered in some instances prior to the use of these drugs. In 1911, Harbitz reported eighty-seven cases of actinomycosis involving the thorax and lungs with 100 per cent mortality. In 1930, Good of the Mayo Clinic reported that this type of infection was almost uniformly fatal. Two years later, Wangensteen commented on the fact that all cured patients except one had had some form of surgery, such as rib resection, drainage of abscesses, and thoracoplasty.

Poppe reports on nineteen patients seen in the Barnes Hospital over a period of years, in seven of whom the disease was apparently arrested. In these seven patients some type of rather radical surgery was used in conjunction with either x-ray, thymol, penicillin, or the sulfonamides. Iodide therapy was not used in these cases.

Apparent cures have been reported from a variety of medications, and it is probably true that the situation is somewhat analogous to the treatment of pulmonary tuberculosis. Proper combinations of surgery to drain secondarily infected abscesses with chemotherapy offer good results if the patient is seen early enough.

Just which drug is best is not completely clear, but the best results have been obtained recently with penicillin, or with a combination of penicillin and sulfonamides. Abrahams and Miller report that penicillin has a greater inhibitory effect in in vitro experiments than sulfathiazole or sulfadiazine. Strains of *Actinomyces israeli* recovered from human subjects were grown in glucose nutrient agar containing varying concentrations of sulfathiazole and sulfadiazine. Some growth-inhibitory effect was noted in levels of from 10 to 20 mg. per cent, but the effect was thought to be too slight for much therapeutic use. On the other hand, penicillin definitely inhibited growth in levels of 0.1 and 0.2 unit per milliliter of medium. This level is within therapeutic range in human beings.

Since actinomycosis is a disease characterized by long latent periods, followed by recrudescence, it is justifiable to state that several years should elapse before the disease is called cured rather than arrested.

To sum up the attitude of most clinics at the present, the following can be said:

1. Pulmonary actinomycosis with involvement of the chest wall is no longer to be considered a hopeless disease.

2. Therapy should consist of a varied attack. Abscesses should be adequately drained; rest for the patient and for the involved area in particular should be utilized.

3. Some patients will respond to internal medication alone, but this should not be relied upon to violate established surgical principles. The medical and surgical treatment of tuberculosis is analogous.

4. At the present, penicillin probably offers the best chance for cure. The simultaneous use of sulfadiazine helps with secondary invaders which may be resistant to penicillin.

DR. CHESTER W. EMMONS.*—I have seen this patient only once before and have little to add to the discussion. The diagnosis of actinomycosis in this patient rests upon the demonstration of actinomycotic granules from one specimen obtained by aspiration of one of the subcutaneous lesions. I saw the section of this material only under a moderate magnification, and while it appears to me to be typical of actinomycosis, I should like an opportunity to examine a Gram-stained section with an oil immersion lens to rule out the possibility that this is a granule of, for example, staphylococcic actinophytosis (botryomycosis). However, this has no doubt been done in the hospital laboratory.

It would be helpful in confirmation of the diagnosis if cultures could be isolated. Since the lesions were not draining and sputum was not available when I saw the patient a week ago, we made cultures from the venous blood on

*Principal mycologist, National Institute of Health.

the improbable chance that there had been a hematogenous spread and that actinomyces still might be present in the circulating blood. This occurs in rare cases, but the cultures in this case have remained sterile.

I think that the clinical course in this patient has not been typical of actinomycosis. If the patient has had pulmonary actinomycosis since the onset of the present illness, it would be expected that a draining sinus tract would have developed through the thoracic wall. I understood that there was no x-ray evidence of continuity between the pulmonary lesion and the substernal abscess, although x-rays were taken during and at the height of development of the latter. Both the subcutaneous lesions have ceased to drain now. Is it possible that these lesions followed hematogenous or lymphatic dissemination from a transitory maxillary lesion? It would be desirable to continue attempts to obtain sputum, and to study additional gastric washings in order to shed more light on the nature of the pulmonary lesions.

Since pulmonary actinomycosis has such a grave prognosis, it is surprising to see this patient in her present condition. Therapy so far has not been directed toward actinomycosis, as I understand, and penicillin and other drugs she has received in the past have not been given in sufficient amounts and over long enough periods of time so that a response would be expected in actinomycosis. It may be, however, that the penicillin she has received has been of some benefit, and since several reports during the past three years have indicated that actinomycosis responds to penicillin therapy, its continued use in this case seems justified.

DR. E. CLARENCE RICE.—The aspirated material from the fluctuant mass was smeared and cultured, and no mycelial elements were found. It was only after some of the material was placed in formalin and paraffin sections prepared that the typical granules of mycelial growth were found (Fig. 2). These are the typical "sulphur granules" seen in infections due to *Actinomyces bovis*.

This is the second case of actinomycosis which we have had at Children's Hospital. In the other patient the actinomyces were found in a biopsied specimen.

On a number of occasions we have found similar bodies in the crypts of removed tonsils when sections were examined microscopically. This apparently is not an uncommon finding, and these bacteria are probably saprophytes.

4. Conference on Acute Regional Enteritis

DR. GEORGE WILLIAM WARE.—D. D., an 8-year-old white boy, was admitted to Children's Hospital, on the service of Dr. William O'Donnell, on November 24 complaining of a sore throat. Two weeks previously a diagnosis of scarlet fever had been made, for which sulfadiazine and later penicillin were given. A papular rash appeared a week before admission and persisted.

Family history and past history were negative except for a pyloroplasty at the age of one month.

Physical examination upon admission revealed a young boy who was acutely ill and in obvious discomfort. The buccal and pharyngeal membranes were

fiery red in appearance. The right tonsil was covered with an exudate. A papular rash was present over the extensor surfaces of both arms and legs and the entire face, and was noted to blanch on pressure. The remainder of the physical examination including the abdomen was negative. Urinalysis revealed 15 mg. of albumin, a trace of acetone, and on microscopic examination there were a few white blood cells with clumps. The red blood count was 3.6 million with 9.5 Gm. of hemoglobin. The white count was 12,300 with 80 per cent neutrophiles, of which 64 per cent were segmented forms, 14 per cent band forms, and 2 per cent young forms. There were 16 per cent lymphocytes, 2 per cent eosinophiles and 2 per cent basophiles.

Fig. 1.—Illustration showing the area of inflamed ileum proximal to its junction with the cecum.

Penicillin therapy, 100,000 units every three hours, was immediately instituted and supplemented by the use of Elixir Benadryl. On the following day the temperature was 104° F. and pulse 120. The rash seemed to have improved somewhat. On the second hospital day the improvement continued, and the patient was placed on a soft diet. That evening he complained of abdominal pain of a generalized nature, which gradually increased in severity during the subsequent twenty-four hours. On the fourth day of hospitalization, the child commenced to vomit and had six watery bowel movements. The abdominal pain continued, and moderate diffuse abdominal rigidity with some distention became evident. The white blood cell count was now 13,700. The differential count showed 79 per cent neutrophiles (73 per cent segmented and 6 per cent band forms), 19 per cent lymphocytes, and 2 per cent eosinophiles.

The patient was seen in surgical consultation by Dr. Robert Coffey, and a diagnosis of ruptured appendix with diffuse peritonitis was made and an immediate operation advised. Preoperatively, 250 c.c. Hartmann's solution containing 5 per cent glucose were given intravenously.

Under nitrous-oxide ether anesthesia, a lower right rectus incision was made. On entering the peritoneal cavity, a strikingly large amount of free serosanguineous fluid was encountered, 750 c.c. being aspirated. The small bowel, beginning in the distal jejunum and terminating abruptly at the ileocecal valve, was of a fiery red color, slightly edematous, and the mesenteric nodes of the involved area were slightly but not notably enlarged (Fig. 1). The mesentery of the involved bowel was not appreciably thickened, and its vascularity did not appear abnormal. The cecum and appendix were not involved. After deciding against the removal of the appendix, the incision was closed in layers without drainage. Immediately after the termination of the operation the patient was given 250 c.c. of whole blood intravenously.

The postoperative course was relatively uneventful. On the second postoperative day, urticarial wheals were observed on the upper extremities and over the abdomen, and the patient complained of severe itching in these areas. Rather prompt relief was secured by the use of benadryl. The white blood count at that time was 9,400 with a normal differential count. The platelet count was 244,000 per cubic centimeter. The patient was discharged from the hospital on the seventh postoperative day.

During the three-month period since the patient's discharge from the hospital he has recuperated completely, a weight gain of 4 pounds has occurred, and he has no complaints referable to the gastrointestinal tract.

DISCUSSION

DR. ROBERT J. COFFEY.—Since the original description by Crohn and his associates[1] in 1932 of chronic regional enteritis, much has been learned about the clinical manifestations, course, and prognosis of this disease. It is essentially a disease of youth, involving in its chronic form any part of the jejunum, ileum, or right colon in a cicatrizing granulomatous process with a decided tendency toward the formation of internal and external fistulas. This chronic form of the disease is the one most frequently encountered and has been studied thoroughly. The acute manifestations of the disease, on the other hand, have seldom been studied pathologically since resection at this stage is seldom attempted. That such acute manifestations of the disease bearing his name did occur was well recognized by Crohn, and since then numerous cases have been reported. Erb and Farmer[2] pointed out that the occurrence of hemorrhagic edema of the ileum with conspicuous regional lymphadenopathy represents an early phase of regional enteritis and is characterized clinically by its similarity to acute appendicitis.

Whether all such cases of acute enteritis represent an early stage of chronic regional enteritis is a debatable point. Because of the occurrence of a rash preoperatively and the development of urticaria postoperatively, an intestinal anaphylactoid or allergic reaction was considered when the markedly hemor-

rhagic condition of the involved bowel with serosanguineous peritoneal fluid was observed. However, the sharply segmented area of involvement pointed to a true regional enteritis.

It has been suggested that true acute regional ileitis may be distinguished from nonspecific acute enteritis by the absence of enlarged mesenteric lymph glands in the latter.[3] However, since so little is known concerning the etiology and pathogenesis of acute regional enteritis, it seems illogical to apply any such criterion. Usually the involved bowel is reddened, thickened, and edematous, and the glands are conspicuously enlarged. Free peritoneal fluid is generally present and may be serous or serosanguineous. Cultures of this peritoneal fluid and of the involved mesenteric glands have been consistently negative. The terminal ileum is usually the site of maximal involvement, while other areas in the jejunum, proximal ileum, or right colon may be affected in continuity or in a patchy manner.

Prior to Crohn's work, the acute form of this disease had been seldom described, and the chronic manifestations were usually considered to be tuberculous. This latter etiological factor has been definitely excluded as a result of many studies.[4] The similarity of the pathologic manifestations in this condition to those found in Boeck's sarcoid have been interpreted as indicating a possible etiological relationship. Erskine[5] has observed the association of acute appendicitis and acute terminal ileitis in several instances and is of the opinion that both may be due to primary involvement of the mesenteric lymph nodes. This is in keeping with the experimental work of Reichert and Mathes,[6] who were able to produce somewhat similar lesions in experimental animals by the injection of sclerosing solutions into the mesenteric lymphatics. However, subsequent investigators failed to substantiate these results.[7]

Since in its chronic form this disease occurs in early adult life, it is probable that the acute manifestations of the disease will be encountered in childhood and youth. Rose[3] refers to acute cases of the disease occurring in children of the ages of 5, 6, and 10. In the series of Fallis,[8] the youngest patient in whom the chronic disease was identified was 9 years old. Koop and his associates[9] have recently reported a case of the chronic form of the disease in a newborn infant in whom the pathologic examination of the involved bowel revealed the typical changes of chronic regional enteritis.

The most important consideration in acute regional enteritis is the prognosis. Crohn[10] encountered eleven patients with the disease, of whom eight did poorly, six being eventually operated upon. However, most of the other reports have been less pessimistic in regard to the outcome.[3, 11, 12] Smithy[13] feels that a spontaneous cure follows in most acute cases and that progression to the chronic form of the disease seldom ensues. A true picture of the ultimate outcome of these cases, however, depends on long and careful follow-up studies.

It is generally agreed at this time that in the chronic form of the disease a sidetracking operation, either with or without resection of the involved bowel, is necessary. There is similar agreement that conservatism should be employed when acute regional enteritis is encountered. Inasmuch as the majority of patients with the acute form are operated on under an erroneous diagnosis of

acute appendicitis, the disease is identified on entering the peritoneal cavity. Since a spontaneous cure may be anticipated in the majority of early cases, surgical extirpation of the acutely inflamed bowel or a sidetracking operation is unwarranted. Removal of the appendix may eventuate in the development of a fecal fistula, a fact pointed out in a series studied by Coffey.[14] Mixter[15] and Fallis[8] advise against appendectomy, and certainly this procedure is undesirable if the cecum is involved.

The subsequent management of acute regional enteritis involves careful periodic observations plus recourse to roentgenologic study of the gastrointestinal tract in the event that suspicious signs or symptoms develop. It is our feeling that the use of intestinal chemotherapeutic agents such as succinylsulfathiazole or oral streptomycin is warranted for a month or six weeks following the identification of the acute disease.

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Psychologic Aspects of Pediatrics

SPECIFIC READING DISABILITY

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THERE is a sizeable group of children whose ability to read is well below their potentiality for learning in general as measured by clinical observation and intelligence tests. It is estimated that between 10 and 15 per cent of children in American schools are unable to read at their proper school grade level and yet are able to perform adequately in academic fields which do not require reading. At one time these children were considered stupid, careless, or lazy. Though a number of different conditions contribute to the disability, there is reason to believe that the large majority of afflicted children have a specific defect, probably residing in the central mechanisms governing the language functions, which manifests itself by difficulty in understanding the written word.

The effect of reading disability on the emotional status of the child and on his future emotional and mental development may be profound; and this is especially unfortunate since the condition is remediable. Responsibility for recognizing a reading defect rests primarily on the school. Unfortunately many schools are lax in this respect. It is, therefore, advisable that the physician, in taking histories on children of school age, make inquiries regarding performance at school and investigate difficulties if they are present.

SYMPTOMATOLOGY

Specific reading disability is a syndrome characterized by (1) difficulty in comprehending written language. Associated with this are (2) alterations in lateral dominance, (3) disturbances in speech, and (4) unusual clumsiness. A further characteristic of the clinical picture is (5) the frequency with which language difficulties and alterations in lateral dominance are observed in other members of the family. (6) Emotional disturbances, arising out of the subjects' inability to read, are generally present.

Specific reading disability is sometimes referred to as strephosymbolia, meaning "twisted symbols," as dyslexia, and as developmental alexia. Orton[1] objects to the designation "congenital word-blindness," originally introduced by Morgan,[2] since the condition is not congenital and there is no blindness.

1. The clinical picture presented by the poor reader is fairly uniform. The child has been considered bright—often unusually so—until he enters school. He may have enjoyed being read to and have shown normal interest in numbers and letters. No problem of any sort was evident. During the first two years in school he does not learn to read. Since much of the reading at this level depends on memorizing, the nature of the defect may not be apparent

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until later. If the child goes to a "progressive" school where there is no insistence on reading until the pupil shows a spontaneous interest, the disability may remain unrecognized for three or four years.

At first, only reading and spelling are difficult. There is often reversal of letters, syllables, and whole words. More commonly, individual letters are written backward and sometimes even upside down. The letters "b" and "d" are frequently confused, as are "p" and "q." Words such as "was" and "saw," "on" and "no," are stumbling blocks, and there may be confusion between words like "from" and "form," and "calm" and "clam." In rare instances the child can read only from right to left (mirror reading). This is sometimes associated with mirror writing. The handwriting may be poor, but usually copying is done accurately and neatly. The learning of geography and history are affected, for the child cannot read his assignments. Grades in arithmetic are usually good. Occasionally there is a reversal of digits, as, for example, reading 42 for 24. Later, performance in arithmetic is also affected as the child is unable to read the written problems and cannot follow the directions. The results on written examinations are poor as is all written work. On the other hand, the child may surprise his teachers by his intelligent responses in class discussions and recitations.

2. Alterations in lateral dominance, particularly ambidexterity and mixed dominance, as right-handedness and left-eyedness or left-footedness, are common in children with reading disability. In a careful study of twenty-two subjects, Eustis[3] found that only four were entirely right-handed, eighteen were ambidextrous, and none was left-handed. A high proportion of left-eyedness, amphiocularity (sighting with either eye), and crossed laterality was found in the same group.

3. Speech disturbances are frequently associated with specific reading disability. They were present in about half of the patients studied by Eustis.[3] There may be delay in the age of starting to talk, impure speech or lisp, stuttering or cluttering speech.

4. A considerable proportion of affected children are abnormally clumsy (developmental apraxia or developmental awkwardness). Their movements are jerky, uncoordinated, and bungling, and resemble those of the rapidly growing adolescent who has not yet become accustomed to the changes in his body size and proportions. The condition is evident in early childhood but becomes more prominent during the school years when the child starts to write and participate in games. Presumably the basis for this is mixed dominance. In such instances the child, instead of being able to use both hands with equal skill (ambidexterity), uses both hands equally awkwardly (ambilevousity).

5. That specific reading disability probably has a hereditary basis is indicated by the high incidence of alterations in lateral dominance, speech disturbances, and reading difficulties in other members of the family.

6. Children with this defect are usually anxious and unhappy because they are unable to do their school work as well as their peers. Conscious of their disability and ridiculed by the other children for their mistakes, they approach

reading with the expectation of failure. They consider themselves stupid and inferior, and they may refuse to try to read or even to pay attention in school. They are often restless, hyperactive, and easily distractible. Parental dissatisfaction with school performance and pressure for better work intensify their anxiety, and these emotional factors further interfere with learning.

The child with a reading disability often shows unusual interest in drawing, mechanics, and athletics. He derives pleasure in a normal way from listening to stories and discussions and from conversation.

Specific reading disability, like other difficulties in the language functions, is much more common in boys than in girls. It is estimated that boys are afflicted from three to four times as often as girls.

The age at which specific reading disability is first recognized depends on the teacher's understanding of the difficulty and the alertness and concern of the parents. The usual age is 8 to 14 years. It can however be recognized earlier before the formal teaching of reading is begun if the possibility of a defect is entertained in children with a history of speech difficulty, alterations in lateral dominance, and other instances of disturbances in the language functions in the family.

Gillingham and Stillman[4] describe a number of tests for reading disability which can be used in young children. The tests are designed to measure the child's ability to recall sequences. A row of pictures of familiar objects is presented to the child, and he is then asked to name them. The order in which he recalls the pictures, whether from left to right or right to left or in a haphazard fashion, is noted. Similarly, a row of toy animals is shown. The animals are covered, and the child is asked to arrange a duplicate set in the same order. The examiner starts with three animals and increases the number, one at a time, until the subject shows confusion.

Again, the child is shown a simple drawing, for example, the profile outline sketch of a chair. His attention is distracted for a few moments, and he is then asked to draw the now concealed figure. This is done fifteen or twenty times. Note is made as to whether the figures are reversed or so confused as to be unrecognizable.

A further test is for auditory confusion. The child is asked to repeat detached syllables, and the frequency of reversals is observed.

ETIOLOGY

According to Orton,[1] the basis for specific reading disability is a faulty establishment of dominance in the reading centers of the brain. The process of reading, as well as speaking and writing, is controlled or initiated or overseen largely, if not entirely, from one hemisphere of the brain. Any defect in the dominant half of the brain, however produced, is likely to result in extensive damage to the language functions, while injury to the corresponding area in the other half of the brain generally gives no specific language symptoms whatsoever. The brain hemisphere which has major control over the language functions is also the

hemisphere which controls handedness, eyedness, and footedness. Although there are exceptions, it is the rule that in right-handed people the left hemisphere of the brain is the dominant one, and vice versa.

Persons with a specific defect in reading are usually able to see and to interpret objects correctly. It is only in the complex function of word recognition that any obstacle is encountered. The difficulty is not one of vision but of comprehension.

Eustis[3] subscribes, in the main, to the thesis of Orton. He looks upon specific reading disability as a familial syndrome associated with ambidexterity and speech defects. He would separate poor readers of this type from the children who fail to read for a multiplicity of other reasons—physical, mental, emotional, educational, and social.

The nature of the disturbance in the cerebral mechanisms which regulate recognition of the written word is not clear. There are no demonstrable organic changes in the brain. Orton[1] offers as an explanation a "faulty establishment of dominance in the reading centers of the brain." It is conceivable that, in a certain number of cases, there may be simply a retardation in development similar to what occurs in children who are slow in beginning to talk. There is variability in all biologic attributes. Children vary in the age at which they are ready to sit up, stand, walk, be toilet-trained, etc., just as they vary in body size, body proportions, and facial features. The age at which children are ready to learn to speak differs widely. Whereas the use of words ordinarily begins in the first half of the second year of life, there is a fairly large number of mentally normal children who are unable to talk until they have passed their third birthday. Similarly, most children of normal intelligence are ready to learn to read at 6 years. In a certain proportion, the age of readiness may be much later, but these children ultimately catch up with the average child and learn to read normally, in much the same manner as children who begin to speak late. Unfortunately in the case of reading the interference of parents and teachers and the child's own feelings of inadequacy introduce emotional factors which interfere with learning.

Emotional Factors.—Children who are unable to read are almost invariably emotionally disturbed. Indeed there are some who believe that the personality disturbance is the paramount and central factor and that emotional difficulties antedate the disorder.[5] The child who is expected to read before he is developmentally ready is in the same position as the child who is expected to respond to any other training procedures before he is ready. The parents are disappointed with the child's performance, and they exert pressure for better work. The child is frustrated by his inability to live up to parental expectations and is discouraged by the criticisms of his parents and teachers and by his failure to keep pace with his fellow students. Any attempt at reading is approached with anxiety, and the child comes to feel stupid and inadequate. He may react with an assumed indifference, with bravado, with hypermotility and distractibility, or with dejection.

Method of Training for Reading.—One reason for the increased frequency of specific reading disability is the use of the "sight" method for teaching chil-

dren to read instead of the "phonic" method. By the older phonic method, children were taught the sounds as well as the forms of the individual letters. By the newer sight method, the children are expected to grasp the meanings of whole words. The normal child learns to read more quickly by the new method, but the child with a reading disability is at a great disadvantage. The greater frequency of reading disability in America has been attributed to the widespread use here of the sight method. The condition is much less common in Germany, where the phonic method is used and where, in addition, the phonetic spelling is more rational.

Training for Handedness.—It is possible that the custom of encouraging the ambidextrous child to use both his hands as he pleases is a factor increasing the incidence of specific reading disability.

Opinions differ as to whether choice of the dominant hand determines the side of the brain which will lead and which will contain the language centers, or whether brain localization is the determining factor. Nielson[6] states that "brainedness comes first." He attributes the occasional instances of right-brainedness in right-handed persons to a shift from natural left-handedness to right-handedness. However, this fails to explain the occasional occurrence of ipsilaterality of handedness and brainedness in left-handed persons, since this would necessitate the training of a naturally right-handed person to the use of his left hand.

Nielson prefers the terms major and minor to the usual designations of dominant and recessive when applied to the hemispheres of the brain. Though the hemisphere which is to lead is hereditarily determined, there is no essential difference between the functional capacity of the two hemispheres at birth. It is for this reason that, in cases of severe trauma to the major hemisphere early in life, the minor hemisphere invariably takes over the function of the major.

Phelps,[7] in discussing the management of the child with hemiplegia, urges that when the dominant hand is handicapped, no exercise whatsoever should be given to it. He believes that manipulation of the affected limb interferes with the development of cerebral dominance on the uninjured side of the brain. In his experience, mental retardation, speech difficulties, seizures, and behavior disorders of all types are much more common in children with right hemiplegia than in those with left. He advises against treatment of the affected arm unless one is perfectly sure that it is not the dominant one.

Contrary to the opinion of most neurologists, Blau[5] contends that cerebral dominance is determined culturally. The potentiality for one or the other cerebral hemisphere to lead is an inherent human property, but the choice of which side is to lead depends on the experience of the individual. Early handedness sets the location of the cerebral language centers.

It would appear from these differing views that, whether or not it is the rule that handedness determines cerebral dominance or vice versa, the choice of the master hand by the young child can, under certain circumstances, determine which side of the brain will lead. It seems reasonable, therefore, to encourage the use of one or the other hand in children who appear to use both hands with equal or nearly equal dexterity, so that cerebral dominance will

be established in one or the other cerebral hemisphere. Orton[1] advises that in the group of children who are not developing a selective skill in either hand or in whom the balance is close, the skill and habit of use of the hand which has the greater capacity be increased. The so-called ambidextrous person is usually a native sinistral who has acquired a considerable measure of skill in certain right-sided activities. In many instances there is no apparent harm from training on the two sides, but it seems likely that even the very skillful ambidextrous individual would have been more facile had he been trained electively in accordance with his natural bent.

DIFFERENTIAL DIAGNOSIS

Specific reading disability should be suspected when a child is not doing as well in school as one would anticipate from his general intelligence, especially when the difficulty relates specifically to reading and spelling. Other diagnostic possibilities are mental retardation, ocular or auditory defects, and emotional blocks. The diagnosis is established by psychologic tests which show a discrepancy between performance on a general intelligence test and on a reading test.

Visual Defects.—Visual defects account for a certain proportion of poor readers. Romaine[8] lists the ocular blocks in reading disability under five headings: (1) general physical disabilities having ocular manifestations; (2) diseases of the eye; (3) errors of refraction; (4) motor anomalies of the eye; and (5) aniseikonia, a condition in which the ocular image received by one eye differs in size and shape from that seen by the other.

Any severe, general, lasting illness may lead to rapid tiring of the eyes with loss of ability to accommodate for reading. With fatigue of accommodation there is often loss of power of convergence, which is essential for simple binocular vision.

With errors of refraction the child gets a blurred image and is unable to distinguish the printed letters. Reading is slow, there are many mistakes, and comprehension is poor.

Defects in the coordination of the two eyes and in eye muscle balance are found occasionally in children who read poorly. For normal binocular vision, both eyes should focus on the object, and the two images should be fused in the brain. When fusion is incomplete, the images perceived by the two eyes overlap or one is seen above the other, and this will necessarily cause considerable confusion in reading.

When the visual images received by the two eyes are of different size (aniseikonia), there may be a definite block to normal functioning of the eyes. Romaine[8] has observed improvement in a relatively large percentage of patients with reading disability after this condition has been corrected with lenses.

Park[9] reviewed the ocular findings in 133 children with dyslexia. A fourth of the children were ametropic. Abnormal motility was rare. The incidence of extremely weak or absent stereopsis (vision for depth) was high (22 per cent). Almost half of the children were heterophoric. Though fusion ability was present in practically all the children, Park found that weak fusion amplitude,

especially weak recovery ability from dyplopia, was definitely associated with dyslexia. As a consequence, an unusual amount of nervous energy is required to adjust the foveal positions constantly in order to achieve a single image.

Sensitiveness to visual defects varies widely in different individuals. Some are aware of the slightest defect; others may carry a severe defect for a lifetime without complaint. A person carrying a visual defect without symptoms may become aware of his limitation only when the general health weakens and the load becomes greater than can be handled.

Children rarely complain of ocular symptoms. Unable to localize their difficulties, they simply refuse to read, and, in time, psychologic blocks are added to their ocular disabilities.

Defective Hearing.—Defective hearing may delay the child in learning to read. This is a greater handicap when the auditory or phonic method is used in training than with the sight method. The child hears blurred or indistinct sounds, is unable to associate them with the words being read, and cannot recognize them later. When there is only partial deafness, this may be entirely missed until the child enters school. Deafness should be suspected if the child constantly asks for repetition of directions.

The usual tests for hearing will disclose most hearing defects. The audiometer is useful in detecting the rare cases of regional deafness where the deafness affects mainly the tone range covered by human speech. It will also reveal cases of developmental word deafness where there is difficulty in recognition of the spoken word. In these children the audiometer gives a normal picture.

PROGNOSIS

The large majority of poor readers who receive ordinary educational opportunities sooner or later learn to read as well as others, and many achieve positions of eminence in academic fields. It is possible that the defect persists, but with increased intelligence and experience, the subjects make adjustments which permit them to read normally. However, improvement can be hastened by proper training, and, in this way, much unhappiness can be avoided. Moreover, a small proportion of poor readers never learn to read unless they receive special training. From conversations with adults who have been poor readers during childhood it seems likely that, in a certain number of individuals, the defect is outgrown in much the same way as impurities in speech, which are so common in children, are mastered later on.

MANAGEMENT

The parents of the child with a reading disability should have some understanding of the nature of the defect. They should know that the child's failure is not due to any fault of his own. Comparisons with siblings and other individuals should be avoided and pressure for better work discontinued. Every effort should be made to restore the child's self-confidence.

Defects in hearing and in vision should be corrected as far as possible. Orthoptic training or exercise of the eye muscles improves poor fusion due to muscle weakness and is beneficial in these cases.

Remedial work should be undertaken only by a teacher familiar with the field.[10] Improvement is related to the pupil's willingness to learn, and it is sometimes weeks or months before the emotional blocking can be broken down sufficiently so that the child is willing to try to read. Thereafter progress is rapid. Instruction should start at the child's reading level, but the content should be interesting and suited to his age. Only harm can be done by presenting a 10-year-old with primers or the usual first-grade readers, no matter how poor his ability.

There are at least three approaches to the teaching of reading: the visual, the auditory, and the kinesthetic. All should be used in remedial work. Through the visual method the pupil is taught to perceive the general shape of words, whether they are long or short, tall or low. In this way he learns to distinguish words from one another in the same way as he distinguishes pictures of a house and a chair, etc. The first letter also gives a clue to the word and, similarly, word endings help.

The auditory or phonic technique consists of teaching the child to analyze and recognize certain familiar units by their sounds. Thus "black," "blue," and "bloom" all have the familiar "bl" sound, and "Jill," "hill," and "fill" all rhyme. By this method larger words are broken down into small units. The kinesthetic or motor discrimination method means tracing words, copying letters in their proper sequence, feeling block letters, and feeling the position of the tongue and the lips while pronouncing words. This valuable technique is often neglected.

By analyzing the pupil's errors, the trained teacher will be able to formulate the most suitable pedagogic approach. A proper remedial program will stress the phases of reading in which the pupil is deficient but should, at the same time, include other training methods.

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Comments on Current Literature

MEGALOBLASTIC ANEMIA

THE January, 1948, issue of *Blood* is devoted in its entirety to megaloblastic anemia, with special emphasis on pernicious anemia. These articles are the first of a series of some eighty articles to be published in honor of Dr. George R. Minot. One article of the current series, "Pernicious Anemia From Addison to Folic Acid," by Russell L. Haden[1] is an excellent review, which gives the historical highlights from the time of Addison to the discovery of folic acid. Haden points out that it was the work of Castle which furnished the final proof that pernicious anemia is a deficiency disease dependent primarily on a gastric defect. This author summarizes the various methods of therapy, stating that while many attempts had been made through the years, no single specific substance, responsible for the beneficial effect, had been isolated. Meanwhile folic acid, a single chemical substance, present in liver, yeast, spinach, and grasses, was shown to be effective to some degree in macrocytic anemias.

In a discussion of "Pernicious Anemia, Nutritional Macrocytic Anemia, and Tropical Sprue" Lucy Wills[2] reviews the entire subject, and stresses the point that a single symptom complex, such as that of a macrocytic hyperchromic anemia, may be a part of many different disease entities. Of particular interest to the pediatrician are the comments on nutritional macrocytic anemia. While Dr. Wills, working in India, had not seen a case in a young child, she refers to the reports of Giglioli[3] in 1934, in which six out of fifty-one patients described were below the age of 12 years, the youngest being 11 months old. In a discussion of treatment, Wills states that until the hemopoietic activity of folic acid was discovered and its conjugated forms gave workers a chemically pure active component, no pure substance with similar activity was available. However, she emphasizes the fact that while folic acid has brought about remarkable hemopoietic responses in all three forms of anemia (pernicious, nutritional macrocytic, and tropical sprue), in general completely normal blood levels have not been restored.

Recently Zuelzer, Newhall, and Hutaff[4] have described megaloblastic anemia of infancy which is characterized by changes in the blood and bone marrow resembling those of Addisonian pernicious anemia, and which showed specific response to folic acid. Fifteen patients ranging in age from 5 weeks to one year were studied. Eleven of the fifteen had histamine-resistant achlorhydria, and macrocytic anemia of varying degree was present in all cases. Hemoglobin levels on admission ranged from 1.7 to 8.3 Gm. per 100 ml. Folic acid was administered by intramuscular injection in all except two instances, the daily dosage varying from 10 to 100 mg., and the total dosage, from 50 to 900 mg. The average course of treatment consisted of two daily injections of 10 mg. over a period of one week. To two patients folic acid was given by mouth in daily doses of 5 mg. for a ten-day period. In every case a characteristic increase in reticulocytes, up to 23 per cent, took place about the fifth day after initiation of therapy. Red cell counts and hemoglobin levels rose significantly. Careful bone marrow studies revealed that in response to folic acid therapy, most of the significant changes took place during the first five days after treatment.

The progression of marrow changes in such an early response to folic acid is summarized by Zuelzer and his associates as follows: "The megaloblasts lose their characteristic structure, and in twelve to twenty-four hours the erythroblasts assume an appearance intermediate between that of megaloblasts and

normoblasts. Typical normoblasts can already be seen in small numbers. Almost the only megaloblasts still recognizable at this time are late, oxyphilic cells, and these disappear at the end of thirty-six hours. Two days after treatment has begun the transformation is virtually complete and the marrow is normoblastic."

The change in the cellular characteristics is accompanied by an increase of basophilic and, slightly later, of polychromatic cells and by the appearance of numerous mitotic figures. Gradually the distribution of erythroid cells approaches the normal.

According to these authors there is definite evidence that, in the absence of sufficient hemopoietic principle, erythroblasts undergo progressive aberration in structure, as well as function, and that the process is reversible except in cells permanently incapable of mitosis. The lack of hemopoietic principle leads to a disturbance in mitosis, which unless too long continued, responds to specific therapy by a prompt return to normal. In the experience of Zuelzer and his co-workers, folic acid brings about such a return to the normoblastic type of erythropoiesis.

This experience concerning the effectiveness of folic acid in the treatment of megaloblastic anemia of infants and young children is shared by Siebenthal,[5] who reports two cases in children aged 6 and 17 months, respectively. Siebenthal concludes that "Megaloblastic anemia is a relatively common disease of white infants, and, since a complete and permanent recovery can be effected by folic acid therapy, the condition should be understood by all those caring for small children."

In an article entitled, "Further Observations on the Specificity of the Folic Acid Molecule," Spies and his associates[6] gave a detailed account of investigations concerned primarily with the mechanism of action of folic acid. These workers undertook a comparative study of the hemopoietic properties of six compounds somewhat related to folic acid in their chemical structure, as shown in persons with Addisonian pernicious anemia, nutritional macrocytic anemia, and tropical sprue in relapse. Of these compounds, only the magnesium salt of formyl pteroyl glutamic acid was effective in producing reticulocytosis and an increase in red blood cells, hemoglobin, while blood cells, and platelets, and this compound was not so effective per unit of weight as folic acid itself. These observations by Spies and his co-workers emphasize the great specificity of the folic acid molecule.

The availability for study of folic acid, a chemically pure substance with remarkably beneficial effects on patients suffering from megaloblastic anemia, offers hope for a more complete understanding of hemopoiesis. Although megaloblastic anemia has been considered of rather rare occurrence in infants and children, it appears that more such cases of anemia occur in this age group than were recognized previously.

RUSSELL J. BLATTNER

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News and Notes

Dr. Julius B. Richmond, of the University of Illinois College of Medicine, is one of the sixteen young scientists appointed as the first group of Scholars in Medical Science, under the plan announced last fall by the **John and Mary R. Markle Foundation** to support qualified young scientists who wish to make a career in academic medicine. Dr. Richmond's field of research is pediatrics. The grant is made to the University of Illinois College of Medicine, Chicago.

The Foundation has allocated a total of $400,000 to accredited medical schools, each school to receive $25,000 payable at the rate of $5,000 annually for five years. As faulty members of the participating medical schools, the Scholars will devote the next five years to teaching and research, at the end of which time they will have had an opportunity to become established teachers and investigators.

A postgraduate refresher course in general pediatrics will be given the week of May 24 through May 29 by the staff of the Department of Pediatrics of the Washington University School of Medicine. The fee is $25.00. A detailed circular may be obtained from the registrar of the school, 4580 Scott Avenue, St. Louis 10, Mo.

On February 2, Dr. Lawrence E. Goldman, a member of the staff of the Children's Hospital and the Washington University School of Medicine, Department of Pediatrics, died at the age of 44.

An **International Congress on Mental Health** will be held in London, England, Aug. 11 through Aug. 21, 1948. There will be three International Conferences, one of which on "Child Psychiatry," with the theme of personality development in its individual and social aspects with reference to aggression, will run from August 11 to August 14. An executive committee of the International Committee for Mental Hygiene, 1790 Broadway, New York, is coordinating preparatory activities in the United States. Inquiries as to further information, application forms, and travel arrangements should be sent to the Executive Office of the Committee, Dr. Nina Ridenour.

The National Foundation for Infantile Paralysis announces the **First International Poliomyelitis Conference,** to be held at the Waldorf-Astoria Hotel in New York, July 12 through July 17. The American Pediatric Society and the Academy of Pediatrics are among the scientific societies sponsoring the conference. Dr. Hart E. Van Riper is the general chairman. There will be ten plenary sessions. The subjects and presiding officers of the sessions are as follows:

1. "The Importance of Poliomyelitis as a World Problem," Oswaldo P. Campos, M.D., Presiding Officer, Clinical Orthopedic Surgeon, Hospital Jesus, Rio de Janeiro, Brazil.

2. "Poliomyelitis: The Early Stage," Rustin McIntosh, M.D., Presiding Officer, Professor of Pediatrics, Columbia University, New York City.

3. "The Management of Poliomyelitis: The Early Stage," Robert Kno-Song Lim, Ph.D., Presiding Officer, Surgeon General, National Defense Medical Center, Shanghai, China.

4. "Poliomyelitis: The Convalescent Stage," Arthur Steindler, M.D., Presiding Officer, Professor of Orthopedic Surgery, State University of Iowa, Iowa City, Iowa.

5. "The Management of Poliomyelitis: The Convalescent Stage," Arvid Wallgren, M.D., Presiding Officer, Professor of Pediatrics, Royal Caroline Medical Institute, Stockholm, Sweden.

6. "The Management of Poliomyelitis: The Late Stage," Carlos S. Ottolenghi, M.D., Presiding Officer, Docente Libre de Ortopedia, Buenos Aires, Argentina.

7. "Bulbar Poliomyelitis," James E. Paullin, M.D., Presiding Officer, Professor of Clinical Medicine, Emory University, Atlanta, Georgia.

8. "Immunology and Chemotherapy in Poliomyelitis," Pierre L. LePine, M.D., Presiding Officer, Director of Laboratories, Pasteur Institute, Paris, France.

9. "The Public Health Aspects of Epidemic Poliomyelitis," Harry S. Mustard, M.D., Presiding Officer, Commissioner of Health, New York City.

10. "Poliomyelitis Throughout the World," Thomas Parran, M.D., Presiding Officer, Surgeon-General, United States Public Health Service, Washington, D. C. Official delegates will be asked to present reports on poliomyelitis problems in their countries.

Details as to accommodation, etc., may be obtained from the Conference Committee, Room 571, Waldorf-Astoria Hotel, New York 22, N. Y.

Book Reviews

Sexual Behavior in the Human Male. A. C. Kinsey, W. B. Pomeroy, and C. E. Martin, Philadelphia, 1948, W. B. Saunders Co., 804 pages. Price $6.00.

Some ten years ago Dr. Kinsey, professor of zoology at Indiana University, became interested in human sexual behavior as the result of his inability to find educational material based on facts rather than on opinion and preconceived ideas of what sexual behavior should be. This interest gradually developed into a remarkable study, which in recent years has been financed by the Rockefeller Foundation. Some 12,000 detailed histories of sex life have been obtained in personal interviews by Dr. Kinsey and his associates, a number which they plan to expand to 100,000. This report is the first of a series of eight planned volumes analyzing the material, and is based on the data obtained from 5,300 white males. The first consideration is the validity of the data and their statistical analysis. This is gone into in detail in the first four chapters, and one can conclude only that the data presented are valid. While data based on many more thousands would undoubtedly lead to some differences in the figures, we doubt very much if the changes would be of any importance.

The material is presented in an objective way, and the authors make no attempt to draw conclusions other than those shown by the data, nor to go into the moral and social implications of their findings. It is a difficult book to review without quoting innumerable detailed statistics, and analyzing the statistics is a thing best left to the reader.

The data show that there are enormous variations in the individual pattern of sexual behavior, and that it is practically impossible to define a norm. One of the striking differences in the pattern is found when the data are analyzed according to educational levels. Rural and urban groups likewise show marked differences. Some of the data are quite startling to our preconceived ideas, as, for example, the peak of sexual activity occurring in adolescence and the early twenties. On the other hand, that some 88 per cent of single men in adolescence and early maturity practice masturbation is not startling news to the physician. The data show that some 70 per cent of preadolescent boys have had sex play between the first year and puberty. Another interesting finding is the relatively small part that prostitution plays in the sexual life of the white male. Despite the care with which the data on homosexuality have been presented, we fear they will be misinterpreted. The frequency with which some homosexual experience has taken place at some time in an individual's life does not mean that roughly one in four men is homosexual. The authors state this clearly.

It is a study of tremendous importance, not only to the physician but equally to the educator and sociologist. It cannot help but have an influence on our laws and penology. The findings will undoubtedly be very upsetting to many, particularly those who look upon sexual behavior as a matter coming under the domain of the moral and religious fields. To the physician and scientist, the important thing is that for the first time the facts of sexual behavior are presented. These facts should lead to a much greater tolerance to what in the past as a result of moral teaching has been looked upon as abnormal.

B. S. V.

The Rh Factor in the Clinic and the Laboratory. Edited by Joseph M. Hill, M.D., and William Dameshek, M.D., New York, 1948, Grune and Stratton, pp. 192.

This volume, a special issue of *Blood, The Journal of Hematology*, consists of a series of papers read at the Dallas-Mexico City Congress in November, 1946. Dr. Philip Levine in "A Survey of the Significance of the Rh Factor" reviews the general Rh problem, and R. R. Race presents an excellent résumé of "The Rh Genotypes and Fischer's Theory," describing the CDE or Fischer-Race nomenclature, which is now rapidly supplanting that of Wiener. Among the nine other papers included in the volume, those on "Hemolytic Mechanisms" by William Dameshek and "The Treatment of Erythroblastosis Fetalis by Substitution Transfusion" by Harry Wallerstein are of special interest.

J. V. C.

Pediatria. XVI Curso de Perfeccionamiento 1945. From the Institute of Clinical Pediatrics and Infant Hygiene "Dr. Luis Morquio," Montevideo, Uruguay, 1947, Impresora L. I. G. U., pp. 710.

A collection of papers by the staff of the Morquio Institute, of which Dr. José Bonaba is director. The first section on the infectious diseases contains, among nine contributions, a discussion of B.C.G. vaccination by Dr. Abelardo Saenz. The second section is concerned with the infant, and the third with surgery. A fourth section on "diverse themes," contains an interesting article by Dr. Piaggio Garzon on "puericulture in art" with some fifty-odd illustrations tracing the subject down through the centuries, and one on the muscles in Heine-Medin's disease by Prof. Dr. Victor Escardo Y. Anaya. The scope of the subjects considered in the volume speaks highly for the many-sided interests and scope of the work of the Morquio Institute.

The Foot and Ankle: Their Injuries, Diseases, Deformities, and Disabilities. Philip Lewin, M.D., ed. 3, Philadelphia, 1947, Lea & Febiger, pp. 847. Price $11.00.

The latest edition of this most complete treatise has been uniformly enlarged over the second edition principally by including in the appropriate chapters many observations and conclusions of the military and naval experience during World War II. While worth-while information has been added to the text, the 102 new illustrations are probably the most valuable addition to the book.

Practically every disease, injury, new growth, and deformity of the foot and ankle in all age groups is discussed to some degree; and, while the broad coverage prevents an exhaustive presentation of each subject, the majority are presented in sufficient detail to afford the reader adequate working information. It should be a valuable reference book for the pediatrician and internist because it will afford physicians of these specialties a ready consultation on the surgical approach to many problems of the foot and ankle with which they are confronted. It also merits a place on the library shelves of every general surgeon, orthopedic surgeon, and general practitioner.

O. P. H.

Editor's Column

"SEXUAL BEHAVIOR IN THE HUMAN MALE"

OCCASIONALLY a scientific work which is essentially medical in nature has influence and repercussions far beyond the field of medicine. Such we believe will be the case with Kinsey's study of the *Sexual Behavior in the Human Male,* which is reviewed elsewhere in this issue. It throws much light and information on a subject which for centuries has been clouded with taboos, customs, and moral and religious teachings. It will be the cause of tremendous controversy and discussion, and undoubtedly even more as the succeeding volumes of the study of sex behavior appear. Physicians will hold to the view that the presentation of scientific facts is the essential thing, and that the upsetting of conceptions based on what people think should be the facts is of secondary importance. Medical thought will be influenced chiefly in the field of psychiatry. On the other hand, the study will have a decided impact on the social, educational, and juridical fields of thought. It is a book that must be slowly and carefully read and one that is difficult to discuss adequately in a review. The more one studies it, the greater becomes the respect for the sincerity and integrity of Professor Kinsey and his associates. Every physician sooner or later must become familiar with the study.

Some criticism has already been expressed that its circulation has extended so early beyond the medical profession. According to a newspaper report, over 200,000 copies have been printed and distributed within a few weeks after publication of the book. We cannot agree with this criticism, for as has been stated, it is a scientific study whose importance extends far beyond the field of medicine.

THE BRITISH MEDICAL ASSOCIATION PLEBISCITE

The February issue contained an account of the medical controversy in Great Britain, which told of the vote to be taken by the B. M. A. on January 31.

According to press dispatches, British physicians voted overwhelmingly against the medical service plan proposed by the British Labor Government, which is now in power. Eighty-two per cent of the 56,000 members of the association voted, with 89.6 per cent of those voting opposed to the proposed plan. The total vote was 40,816 opposed to 4,735 in favor. A further question as to whether they would accept service under the plan, provided the majority voted against it, was asked of the practitioners and specialists who would furnish the personnel to carry out the plan. The vote was 24,066 (86 per cent) against accepting service and 4,495 in favor. This leaves but 3,560 general practitioners and 971 consultants and specialists to operate the plan for a population of 47,000,000 if the 24,000 who voted against accepting service boycott the act, which is voluntary and not compulsory for the physician.

The B. M. A. was severely and vehemently criticized in the Commons by Minister of Health Bevan, and by a majority vote along party lines the act was sustained in face of the opposition of the British physicians to its present provisions. The government has stated that despite the medical opposition the act will be put into effect on July 5.